Title: Chlamydia infection

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Abstract:

Chlamydia trachomatis ('chlamydia') is the most commonly diagnosed bacterial sexually transmitted infection (STI) worldwide and an important cause of reproductive complications in women and epididymitis in men. Different serovars (types) of chlamydia are associated with different types of infections: A-C cause ocular infections ('trachoma'), D-K ano-genital infections, and the serovars L1-L3 cause lymphogranuloma venereum (LGV). Chlamydia infection is common among HIV infected individuals, but there is little evidence that the infection differs between HIV infected and non-infected individuals. However, there is some evidence that chlamydia infection increases the risk of HIV transmission and acquisition. Chlamydia is most common in young heterosexual adults aged ≤26 years and among men who have sex with men (MSM) with high rates observed among HIV infected MSM. Most infections are asymptomatic, although rectal infection with LGV is more likely to be symptomatic and clinically severe. Annual screening for young sexually active women is widely recommended and annual or more frequent screening is recommended for MSM, HIV infected men and women, incarcerated men and women, sex workers, and those considered at high risk based on sexual history. Chlamydia is easily diagnosed using self-collected specimens - urine specimens, vaginal swabs and rectal swabs. For infection with non-LGV associated serovars, azithromycin 1g as a single dose or doxycycline 100mg twice daily for 7 days the recommended treatments. There is no evidence that treatment efficacy differs by HIV status.

Key words:

Chlamydia trachomatis, Lymphogranuloma venereum, HIV, men who have sex with men, heterosexual, pregnant, screening, treatment, epidemiology, biology

Abbreviations:

LGV	Lymphogranuloma venereum
MSM	Men who have sex with men
NAAT	Nucleic acid amplification test
PID	Pelvic inflammatory disease
POCT	Point of care test
STI	Sexually Transmitted Infection

Introduction

Chlamydia trachomatis ('chlamydia') is the most commonly diagnosed bacterial sexually transmitted infection (STI) worldwide and if left untreated, is an important cause of reproductive and adverse pregnancy complications in women and epididymitis in men. As chlamydia is largely asymptomatic, screening and treatment is the main way to detect cases and reduce transmission. The advent of highly sensitive next generation nucleic acid amplification tests (NAATs) that allow the use of self-collected samples such as urine or vaginal swabs has meant that chlamydia testing has never been easier to conduct. While chlamydia infection is common among HIV infected individuals, there is little evidence to suggest that the course of infection or the risk of acquiring infection differs between HIV infected and non-infected individuals. This chapter will provide an overview of chlamydia infection in adults including its epidemiology, diagnosis and treatment, highlighting any concerns that are particularly relevant to HIV infected individuals.

The biology of *Chlamydia trachomatis*

Basic biology of Chlamydia

Chlamydia trachomatis are small, non-motile, obligate intracellular bacteria that typically infect human eukaryotic columnar epithelial cells. [1] The organism has a unique biphasic developmental cycle that consists of the infectious extracellular spore like forms that do not replicate (called elementary bodies) and intracellular replicative and non-infective forms (called reticulate bodies). [2] This unique intracellular growth pattern means the organism is naturally resistant to many host defense mechanisms and this reduces a host's ability to develop protective immunity against future infection. As a result, repeat chlamydia infection is relatively common in individuals previously infected.

Different serovars (types) of *Chlamydia trachomatis* are associated with different types of infections: A-C cause ocular infections ('trachoma'), D-K ano-genital infections, and the serovars L1-L3 cause lymphogranuloma venereum (LGV), a variant of chlamydia infection that is more common among HIV-infected individuals, particularly men who have sex with men (MSM).

Chlamydia and risk of HIV acquisition or transmission

It is biologically plausible that chlamydia infection increases the risk of HIV transmission and acquisition. It is possible that urogenital or ano-genital chlamydia infection increases the risk of HIV acquisition through disruption of the mucosa facilitating access of the HIV virus to target cells under the epithelial surface, thus increasing the probability that HIV is able to establish systemic infection. [3] A systematic review and meta-analysis of HIV shedding in the presence of an STI found that chlamydia was associated with an 80% increase in the likelihood of detecting HIV in the genital tract (OR = 1.8; 95% CI: 1.1, 3.1) and concluded that conditions that recruit polymorphnuclear leukocytes to the genital tract are associated with an increase in HIV shedding. [4] It has also been found that chlamydia infection is associated with higher HIV viral loads in the genital tract, potentially increasing the risk of HIV transmission. [5] Treatment of chlamydia infection decreases the amount of HIV virus in genital specimens, further supporting a direct mechanism for chlamydia infection increasing viral loads in the genital tract. [6, 7] This highlights the importance of regular STI screening and treatment for HIV infected individuals regardless of gender or sexual practice.

The epidemiological evidence of an association between chlamydia and HIV acquisition or transmission comes mainly from observational studies which are susceptible to confounding and other biases because both chlamydia and HIV are transmitted via sexual practices. There have been two randomised controlled trials (RCTs) of STI treatment (syphilis, gonorrhoea,

chlamydia and trichomoniasis) for the prevention of HIV-1 infection, conducted in Mwanza, Tanzania, and Rakai, Uganda [8, 9]. These studies found no association between treatment for chlamydia and the incidence of HIV-1, however, the results were limited by small numbers of cases of chlamydia detected in both intervention and control arms. A cohort study of women in Zimbabwe and Uganda found some evidence to suggest an association between current or previous chlamydia infection and HIV incidence. [10] Among HIV positive pregnant women, observational data have shown that co-infection with either chlamydia or gonorrhoea is associated with an increased risk of maternal to child transmission of HIV, [11] highlighting the importance of STI screening and treatment for HIV infected pregnant women. Observational data show an association between rectal chlamydia and HIV acquisition with three separate cohort studies in the US and Australia finding strong associations between rectal chlamydia infection and the risk of HIV infection (two to nine-fold increased risk). [12-14] Studies among sex workers in Africa have shown HIV infected women to be at increased risk of chlamydia infection, and in those with lower CD4 counts, to have an increased risk of chlamydial pelvic inflammatory disease (PID). [15, 16]

Epidemiology and natural history of *Chlamydia trachomatis*

Uncomplicated chlamydia infections

Chlamydia is the most commonly diagnosed bacterial STI worldwide. In 2012, an estimated 130 million people became infected with chlamydia. [17] The number of chlamydia cases diagnosed each year in several high income countries has been steadily increasing over the last two decades as chlamydia testing rates increased with over 1.4 million cases diagnosed in the United States in 2014 (Figure 1). However, as over 80% of chlamydia cases in women and men are asymptomatic, most cases will go undetected without testing. In fact, an estimated 2.8 million cases of chlamydia infection occur annually in the United States, twice

as many infections as are diagnosed, with projected total lifetime direct medical costs of $517 million.[18]

In high income countries, chlamydia is most common in young heterosexual adults aged ≤26 years with population-based prevalence estimates of 4.3% for cervical infection in women and 3.6% for urethral infection in men. [19] Chlamydia is also common among MSM attending STI clinics amongst whom chlamydia positivity has ranged between 2 to 5% for urethral infection and 6% to 9% for rectal infection. [20-24] Higher chlamydia prevalence has been associated with social disadvantage [25] and has been higher in people from some minority ethnic groups. [26, 27] In the United States, chlamydia surveillance data show chlamydia diagnosis rates are 5.9 times higher in Blacks, 3.8 times higher in American Indians/Alaskan Natives and 2.0 times higher in Hispanics compared with Whites. [28] Pharyngeal chlamydia infection can also occur with estimates ranging from 1 to 3% in women and MSM. [29, 30] There are few representative data available for chlamydia prevalence among individuals living with HIV, however data from STI clinics show higher rates of chlamydia and other STI among HIV infected MSM. Data from STI clinics in the United States show urethral and rectal chlamydia positivity of 5.6% and 18.6% respectively among HIV positive MSM compared with 6.4% and 8.1%, among HIV-negative MSM.[28]

The increasing uptake of HIV biomedical preventions such as pre-exposure prophylaxis (PrEP) for HIV is likely to lead to further increases in chlamydia and other STIs among MSM in high income countries. Data from studies in the US and Australia are showing increased incidence of rectal STIs among MSM using PrEP. [31-33] An Australian study found an annual incidence of rectal chlamydia of 67.5% [33] with rates of between 33% and 48% observed in US studies. [31, 32] A recent meta-analysis of 18 studies found that MSM using

PrEP were 25.3 times more likely to acquire gonorrhoea, 11.2 times more likely to acquire chlamydia, and 44.6 times more likely to acquire syphilis compared with MSM not using PrEP.[34]

Lymphogranuloma venereum (LGV)

During the 20th century LGV was endemic in developing countries across the tropics where infections mainly involved the genitals with genital ulceration and lymphatic spread, classically resulting in the formation of inguinal buboes. Since the early 2000s, LGV has re-emerged in MSM where infections of the rectum rather than the genitals have predominated. LGV infections among MSM have been mainly due to the L2b variant of *C. trachomatis*. Reports from various countries have linked rectal LGV infections with various markers of increased sexual risk behaviours including: high rates of other concurrent STIs such as syphilis, injecting drug use, and concurrent hepatitis C.[35-37] Rectal LGV has been associated with condomless receptive anal sex, fisting, sex with drugs *('chemsex')* and sharing of sex toys.[36, 38] Rectal LGV infections have also been substantially over-represented in HIV infected MSM [39] and it remains uncertain to what extent this is biological - reflecting immune suppression – or behavioural because of increased sexual risk. Surveys from Europe have shown that rectal LGV accounts for 8-16% of rectal chlamydia infections in MSM.[40, 41]

The natural history of chlamydia infection

Many questions still remain about the natural history of chlamydia infection in men and women and it is unclear whether the natural history varies between HIV infected and non-infected individuals. Cohort studies have shown that if left untreated, most genital chlamydia infections will naturally clear within about 12 to 14 months on average, but some infections

can persist for two, or even three years without treatment. [42-45] Several reviews have examined the risk of reproductive sequelae - PID, ectopic pregnancy and tubal factor infertility - following infection in women, [46-50] but estimates are limited by challenges with study design and lack of gold standard tests for diagnosing these sequelae. Statistical syntheses of available evidence estimate that the probability of clinical PID following an episode of chlamydia is about 16% (95% credible interval 6 to 25%) [51] and the probability of tubal factor infertility is about 1%, with variation depending on age. [52] These models also estimate that the proportion of PID, ectopic pregnancy and tubal factor infertility attributable to chlamydia is 20%, 5% and 29% to 45%, respectively. [53] There is some evidence to suggest that the risk of reproductive tract morbidity in women might increase with repeated infection, [54-56] but it is unclear whether the increase in risk is due to an increase in the cumulative infection time or a higher probability of progression with each subsequent infection. [47] Pregnant women infected with chlamydia have an increased risk of pre-term delivery [57] and vaginally-delivered babies of untreated mothers are at risk of chlamydial conjunctivitis and pneumonitis. [58]

Clinical presentation

There is little evidence to suggest that the clinical presentation of chlamydia infection is different between HIV infected and non-infected men and women.

Males

The majority of uncomplicated chlamydial genital tract infections in males are asymptomatic with detection of infections requiring screening of men who do not have any genital symptoms. In the minority of men with chlamydia who are symptomatic, the symptoms of urethritis include dysuria, urethral discomfort, and/or urethral discharge. Where urethral

discharge is present, it is often clear to white and relatively small in volume in contrast to the discharge characteristically seen with urethral gonorrhoea which is usually purulent – yellow or green – and of often larger volume. Gram staining of a urethral swab will usually demonstrate the presence of polymorphonuclear leucocytes (polymorphs), however this is not specific to chlamydia and can be seen with other urethral pathogens such as *Mycoplasma genitalium*. Polymorphs may be absent with urethral chlamydia. The Gram stain will usually help to differentiate chlamydial urethritis from gonococcal urethritis with Gram negative diplococci present in the latter but absent with chlamydia, unless co-infection is present. Some men with chlamydial infection will develop epididymo-orchitis which is characterised by acute epididymal and testicular pain, swelling and tenderness. Scrotal ultrasound can demonstrate swelling of the epididymis and testis and help exclude differential diagnoses for acute scrotal swelling such as testicular torsion. The effects of chlamydia on male fertility are disputed; some have found no effect, some suggest decreased semen quality, or impaired sperm fertilising capacity and DNA integrity.[59, 60]

Most chlamydial infections of the rectum in MSM are asymptomatic. Symptoms of chlamydia proctitis when present include anorectal pain, discharge and bleeding. Gram staining of an anal swab taken from men with chlamydial proctitis usually reveals the presence of polymorphonuclear leucocytes and can help to distinguish gonococcal proctitis as Gram negative diplococci may be present in the latter. Rectal chlamydia and gonorrhoea may co-exist in men who have sex with men with proctitis.

Females

As with males, most women with uncomplicated, lower genital tract chlamydial infections do not have genital symptoms and require detection through chlamydia screening. Symptoms when present include vaginal discharge, dysuria and irregular vaginal bleeding. In most

women with chlamydial infection the cervix will appear normal. In a minority of cervical infections the cervix is visibly inflamed with cervical erythema, oedema, and cervical discharge. The cervix may be friable with contact bleeding during endocervical swabbing and the woman may report post-coital bleeding. Upper genital tract infection may lead to PID with endometritis and salpingitis. Symptoms of PID include lower abdominal pain, deep dyspareunia and intermenstrual bleeding. These symptoms can be mild and difficult to distinguish from other causes of pelvic pain. The diagnosis of chlamydial PID is clinical: signs of chlamydial PID include cervical motion, uterine and adnexal tenderness, however, these have poor specificity for PID. [61]

There have been increasing reports suggesting that rectal chlamydia is more common among women than previously thought. Anal sex is increasing among heterosexual couples, with population-based data from the UK showing that 15-17% of heterosexual people reported anal sex in the last year, a 2-3 fold increase since 1990. [62] There is also evidence that many women acquire rectal chlamydia infection in the absence of any reported anal sex, [23] raising the hypothesis that there could be autoinoculation of cervical chlamydia infection from the rectal site or vice versa.

LGV

Rectal infection with LGV associated serovars also occurs, particularly among MSM, and may be clinically indistinguishable from rectal infections caused by other pathogens [39, 63] including chlamydial serotypes not associated with LGV. However, LGV is more likely to be symptomatic and may be more clinically severe. [64, 65] After mucosal inoculation, LGV infection spreads through underlying tissue to regional lymph nodes. This contrasts with chlamydial infections due to *C. trachomatis* serovars A-K which are limited to the mucosa.

Exudative proctitis has frequently been observed in patients with rectal LGV via proctoscopic examination. [65, 66] Cases of LGV proctitis can be chronic and present similarly to inflammatory bowel disease leading to misdiagnosis or delayed diagnosis. [67] Asymptomatic rectal LGV also occurs and has accounted for around a quarter of LGV cases in some studies. [64, 68]. LGV in MSM can also cause penile or anal ulceration as well as inguinal bubo formation.

Case illustration

Two HIV infected men who were sexual partners presented together: one with an anal ulcer for several days (figure 2), the other with increasing swelling in the left inguinal region for one month (figure 3). A swab taken from the anal ulcer from one of the men and pus aspirated from the inguinal bubo present in the other. Both specimens tested positive for *Chlamydia trachomatis* by nucleic acid amplification testing. Genotyping of the ulcer and aspirate specimens confirmed the presence of *C. trachomatis* variant L2b confirming the diagnosis of LGV transmission between the men. Both men were treated for LGV with doxycycline 100mg twice daily for 21 days. While the anal ulcer resolved, the inguinal bubo continued to enlarge leading to spontaneously rupture and discharge from a sinus.

Screening and diagnostic considerations

Screening recommendations

Several high income countries including the USA, Australia, Canada and England recommend yearly screening for urogenital chlamydia infection for all sexually active women or both women and men in the age groups at highest risk of infection. [69-73] Local

screening guidelines vary between countries and sometimes within countries. For example, in the United States, annual screening is recommended for sexually active women under 25 years of age, but not for heterosexual men unless they are considered at high risk (e.g. incarcerated or attending an adolescent health clinic or STI clinic). [71] In England, annual screening is recommended for sexually active men and women under 25 years [72] and in Australia, annual screening is recommended for sexually active men and women aged under 30 years. [69] The evidence to support pharyngeal or rectal chlamydia screening in heterosexual men and women is unclear and at present most guidelines do not recommend routine screening for pharyngeal and rectal chlamydia in heterosexual men and women. Any chlamydia screening at these sites should take into account patient risk and local guidelines and recommendations.

Several regional guidelines recommend at least annual screening of MSM for STI including chlamydia with more frequent screening, up to 3 monthly, for higher risk MSM. [61, 74] Screening of MSM should routinely include testing for urethral and rectal chlamydia, with some countries also recommending screening for pharyngeal chlamydia.[74]

Annual or more frequent chlamydia testing has also been recommended for other population groups including: HIV infected men and women, incarcerated men and women, sex workers, and those who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has a STI. [71] Individuals attending with symptoms or reporting contact with a sexual partner with a STI should also have a test for chlamydia and other STIs. A full STI screen should also be considered for individuals diagnosed with chlamydia.

Chlamydia screening should also be considered for pregnant women to reduce the risk of adverse pregnancy outcomes. Some countries have more explicit criteria for chlamydia screening in pregnant women. For example, in the United States guidelines recommend that adolescent and young adult women who are pregnant should be re-screened during their third trimester, regardless of whether or not they tested positive for chlamydia earlier in the pregnancy. This is because of the high risk of chlamydia in these women and the fact that treatment may prevent maternal postnatal complications and neonatal infection. [61, 75]

Routine clinic visits by HIV infected individuals for their HIV management provide an opportunity for STI screening. An opt-out approach to the offer of STI screening for example: 'we offer STI screening to HIV positive patients at least once a year – would you like a check-up,' can reduce the need for a sexual history which some HIV infected patients may feel reluctant to disclose and some physicians uncomfortable to ask. Opt-out screening of HIV infected MSM for syphilis using blood taken for HIV monitoring has for example, been shown to increase syphilis screening and detection in this population. [76] Suitably trained nurses are ideally placed to undertake such STI screening. [77] Reminders that prompt STI screening of HIV infected patients should be tailored and integrated into local medical record systems. [78] Electronic medical records with clinician alerts and automated text message reminders to patients for STI screening have been shown to be effective in increasing STI screening and detection among MSM. [78, 79]

A test-of-cure to detect treatment failure (i.e., repeat testing 3–4 weeks after completing treatment) is not advised for those treated with the recommended regimens (see below), unless adherence is in question, symptoms persist, or re-infection is suspected. The use of chlamydial NAATs at less than 3 weeks after completion of therapy is not recommended

because of the potential continued presence of nonviable organisms [80, 81] that can lead to persistently positive ('false positive') results. However, several countries now recommend a test for re-infection for those diagnosed with chlamydia at three months after treatment because of high rates of repeat infection. [61, 69] Among women, a systematic review reported a re-infection rate of up to 32% (median 13.9%), with younger age being associated with higher rates of re-infection. [82] Among heterosexual men, a systematic review reported an overall repeat infection rate of 18.3% (median 11.3%) for urethral chlamydia infection with 10.9% occuring at the 4 month follow up visit. [83] Studies have found that between 5.9% to 28.2% of MSM treated for rectal chlamydia infection presented with a repeat infection on follow up testing. [84-87] A recent study found no difference in repeat rectal chlamydia infection between HIV infected and non-infected MSM. [88] Most repeat infections are considered to result from re-infection from an infected partner rather than treatment failure.

Specimens and diagnostic assays

Chlamydia infection can be diagnosed in women by testing first-catch urine or swab specimens from the endocervix or vagina. Speculum examination is therefore not necessary unless symptoms are present. Diagnosis of *urethral chlamydia* infection in men can be made by testing a urethral swab or first-catch urine specimen with the latter being less invasive and therefore preferable (Table 1). NAAT tests that identify *C. trachomatis* specific nucleic acid (DNA or RNA) in clinical specimens are recommended because of their superior test performance. [61, 89-91] Provider-collected and patient self-collected vaginal swab specimens have been found to have equivalent sensitivity and specificity with FDA-approved NAATs [92, 93] and women find self-collected specimens highly acceptable. [94] Rectal and pharyngeal *chlamydia* infection can be diagnosed using either provider or patient collected

rectal and pharyngeal swabs respectively. Data indicate that performance of NAATs on self-collected rectal swabs is comparable to clinician-collected rectal swabs, and this specimen collection strategy for rectal *chlamydia* screening is acceptable to patients. [95] However, no manufacturer of chlamydia NAATs has licensed extra-genital specimens (rectal or pharyngeal swabs) for diagnosis. Nevertheless, NAATs are still the preferred tests for these specimens and some NAATs have been validated for these specimens. However, as the sensitivity and specificity can be lower compared with urogenital specimens, confirmation of positive results in an independent assay should be considered. Collecting pharyngeal and rectal specimens should always be considered in MSM and only among heterosexual men and women according to their risk. [61, 91]

As part of their assessment for STI testing, men and women should be asked if they have urethral or vaginal symptoms. MSM should also be asked if they have symptoms of proctitis. Those without genital or anal symptoms can be offered the option of self-collected or clinician collected testing for STI depending on the local clinic protocol, patient and clinician preference. Patients who report genital or anal symptoms should be examined and have STI testing for the appropriate range of pathogens based on examination findings and the provisional diagnosis e.g. urethritis, cervicitis, PID, or proctitis.

Rapid point-of-care tests (POCT) provide a test result at the same patient visit thereby allowing immediate treatment. However, compared to NAATs, the sensitivity of the current, mostly immunochromatographic, rapid POCT is clearly insufficient. [96, 97] However, there is promise for the future with new generation POCT tests using nucleic acid amplification having been recently developed that demonstrate diagnostic accuracy that is similar to that of laboratory NAATs. [98] Until these are available however, the current rapid POCT are not

recommended, unless other more sensitive tests are unavailable; their results should be interpreted with caution.

Screening for LGV

Clinicians should consider LGV as a potential cause for a positive chlamydia result in clinical scenarios where LGV is considered possible. This includes positive rectal chlamydial results in HIV infected MSM and in those presenting with symptoms of proctitis. While many rectal LGV infections will present with rectal symptoms, some will be asymptomatic, with 27% of LGV cases found to be asymptomatic in an STI clinic population in the Netherlands. [68] Genital LGV infection should be considered where chlamydia is detected in MSM presenting with genital ulceration where no other cause for the ulceration is evident. Genotyping is needed to distinguish LGV from non-LGV strains of chlamydia, however there may be a delay before the results of genotyping are available so treatment for LGV may need to be commenced before the results of genotyping are available.

Partner notification

Patients diagnosed with chlamydia should be advised to inform recent sexual partners so partners are prompted to undertake testing for chlamydia and treatment if required. Partner management for chlamydia is intended to enhance the public health control of chlamydia and also to reduce re-infection of patients. In a number of countries local web based services that support notification of sexual partners, including the use of named or anonymous text messages or emails, have been established to support partner notification for chlamydia and other STI. These may be an option for patients who prefer not to inform sexual partners directly. Notification of partners may be difficult where contact details are not available; such may be the case with casual or anonymous sexual partners. Patient delivered partner therapy,

where the patient diagnosed with chlamydia is provided with antibiotics such as azithromycin to take to their sexual partners, may be considered depending on whether local policy and relevant regulations are permissive. [99] If this is employed information should be provided to those partners to optimize management including warnings about possible medication side effects and the importance of chlamydia testing and treatment.

Chlamydia treatment

Treating persons infected with *chlamydia* reduces their risk of continued sexual transmission *and developing* adverse reproductive health complications. Treating pregnant women reduces the risk of adverse pregnancy outcomes and the risk of mother-to-child transmission of chlamydia. Chlamydia treatment should be provided promptly for all persons testing positive for infection. There is no evidence that treatment efficacy differs by HIV status. A recent RCT comparing azithromycin with doxycycline for the treatment of chlamydia urethritis found no difference in efficacy between HIV infected and non-infected men.[100] STI management guidelines in the US, Europe and Australia do not differentiate by HIV status for chlamydia treatment.[74, 101]

Urogenital infection

For uncomplicated genital chlamydia infections with non-LGV associated serovars, azithromycin 1g as a single dose or doxycycline 100mg twice daily for 7 days are the most widely recommended treatments. [61, 91, 102] A recent meta-analysis of randomized clinical trials of azithromycin versus doxycycline for the treatment of urogenital chlamydial infection found that the treatments were equally efficacious, with microbial cure rates of 94% and 97% respectively.[103]

It is important however, to maximise adherence and it has been recommended by some that onsite, directly observed single-dose therapy with azithromycin be available for persons for whom adherence with multiday dosing is a concern. [61] Persons treated for chlamydia should be advised to abstain from sexual intercourse for 7 days after single-dose therapy or until completion of a 7-day regimen and resolution of symptoms if present to minimise transmission to sexual partners. To minimize the risk of re-infection, patients should also be advised to abstain from sexual intercourse until all of their sex partners are treated.

Rectal chlamydia infection

For rectal chlamydia infections with non-LGV associated serovars, azithromycin 1g as a single dose or doxycycline 100mg twice daily for 7 days remain the most widely recommended treatments. [61, 91, 102] However, there is increasing concern about the possibility of treatment failure for rectal chlamydia with repeat infection rates of up to 22% following treatment with azithromycin. [84-87] While most of these are likely to be due to re-infection, there is concern that a significant proportion may be due to treatment failure. [104, 105] A recent meta-analysis examining rectal chlamydia treatment found a pooled treatment efficacy of approximately 83% for azithromycin 1g and 99% for doxycycline 100mg twice daily for seven days. [106] While these results have raised concerns about the effectiveness of azithromycin 1g, the quality of evidence included was poor with no RCTs directly comparing azithromycin with doxycycline identified. However, both regimens continue to be recommended as first-line because of the low quality of the data supporting the superiority of doxycycline over azithromycin for treating rectal infections.

Pregnant women

Treatment with azithromycin 1g is the recommended treatment for chlamydia infection in pregnant women and has been found to be safe and effective. [107] Doxycycline is contraindicated during pregnancy and is not recommended treatment for chlamydia in pregnant women. [107] Test-of-cure to document chlamydial cure by NAAT within 3 to 4 weeks after completion of therapy is recommended for pregnant women in some countries [61] because serious sequelae can occur in mothers and neonates if the infection persists. [57, 58]

LGV

Guidelines recommend doxycycline 100 mg twice daily for 21 days as first line therapy for rectal LGV [61, 108, 109] which is of longer duration than treatments recommended for rectal chlamydia. Several published studies suggest that this should cure nearly all cases of rectal LGV. [41, 110-113] Although rectal infections with LGV associated variants of *C. trachomatis* have been concentrated in MSM, rectal chlamydial infections in MSM are still overall more likely to be caused by other chlamydial serovars. However, doxycycline 100mg twice daily for 7 days or azithromycin 1g single dose which are used for rectal chlamydia may not be adequate for LGV cure, particularly if the LGV infection is clinically severe [110, 114]. This underscores the value of genotyping positive rectal chlamydial specimens in MSM to identify LGV and the need for a longer course of doxycycline. There have been a number of case reports of doxycycline failing to cure LGV in MSM despite 21 days of therapy, including cases of LGV buboes and rectal LGV [115-118]. These suggest that some more clinically severe LGV infections such as those that result in abscess formation require close clinical observation and may require additional therapy. Azithromycin 1 g weekly for 3

weeks has also been proposed as an alternative LGV treatment; however, this is based on very limited data.[112]

Antimicrobial resistance and Chlamydia trachomatis

Despite increasing global antimicrobial resistance among other STIs, [119] antimicrobial resistance of *Chlamydia trachomatis* remains a rare event. [120, 121] Nevertheless, in recent years concerns have been raised over treatment failure in chlamydia infected patients treated particularly with azithromycin 1 g single dose. [122-124] Some of these treatment failures can be explained by re-infection, poor compliance or tolerance of treatment, or detection of nucleic acid from non-viable chlamydia due to re-testing too early after treatment. [104, 105] However, for some, it is unclear why treatment has failed to clear the infection. This highlights the importance of ensuring a test for re-infection is conducted at 3 to 6 months following initial diagnosis and treatment and if any concern about treatment failure, using doxycycline is to be recommended.

Conclusion

Chlamydial infections are one of the most common STI worldwide and occur in HIV infected men and women. HIV infected patients who are sexually active should be screened for chlamydia using appropriate specimens and testing methods. The routine clinic visits that HIV infected patients attend for their HIV care provide an opportunity to offer STI screening that includes chlamydia testing. As chlamydia is likely to enhance the transmission of HIV due to genital or rectal inflammation, identification of chlamydia and treatment may help to limit HIV transmission. Clinicians should be aware of LGV which has re-emerged among HIV infected MSM in particular, and which requires genotyping for confirmation and more

prolonged treatment compared to uncomplicated chlamydia. HIV infected women should have chlamydia treated to prevent adverse reproductive sequelae including mother-to-child transmission of chlamydia and neonatal infection.

Acknowledgements:

We thank Charussri Leeyaphan for providing references and Tim Read for a case report.

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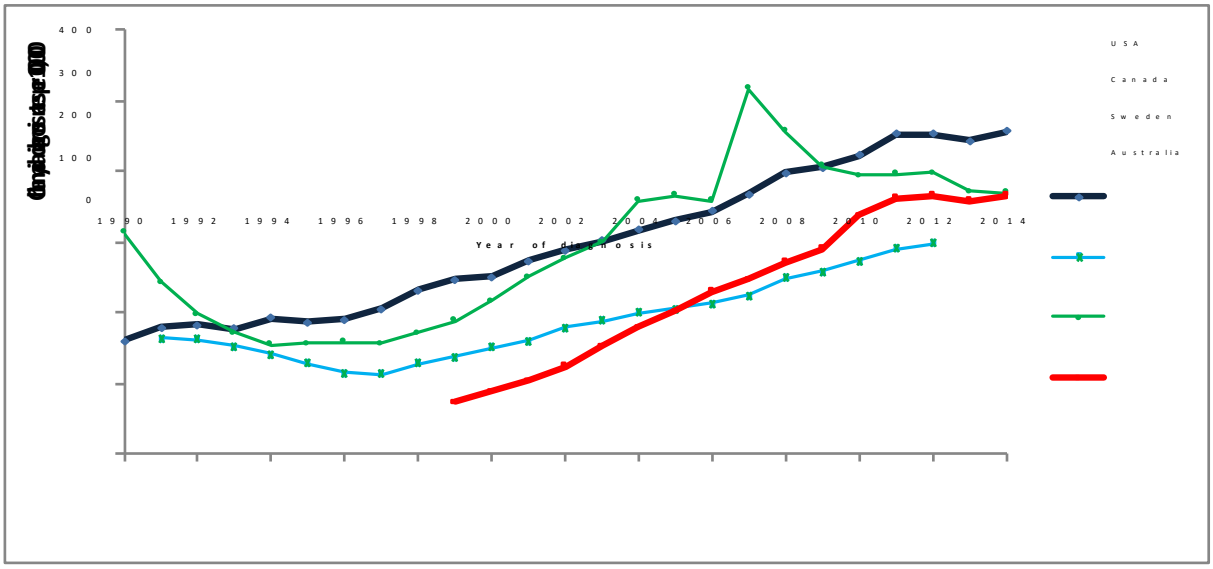

Figure 1: Chlamydia diagnosis rate per 100,000 by year

(Source: USA [28], Canada [125, 126], Sweden [127], Australia [128])

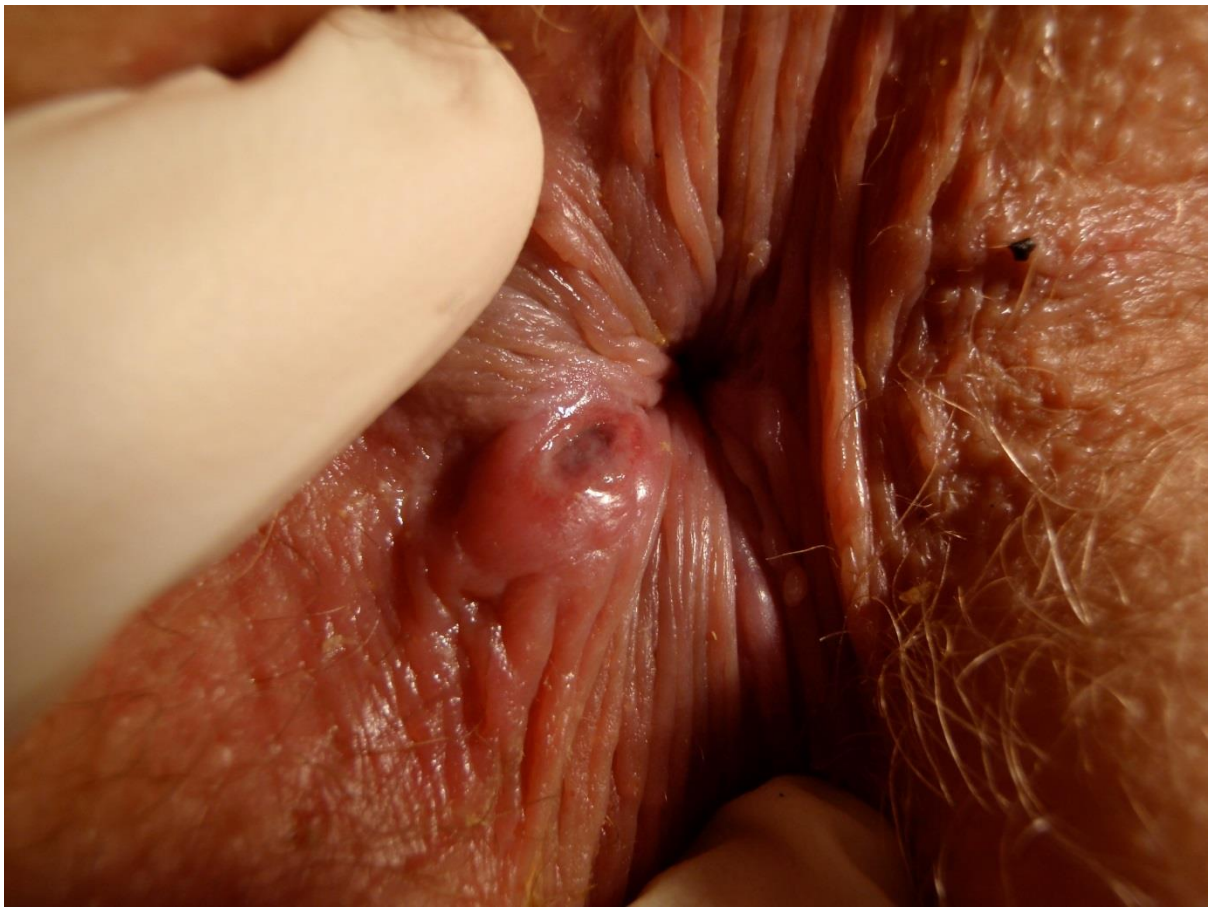

Figure 2: Anal ulcer in an HIV positive male

(*Acknowledgement: Dr Tim Read*)

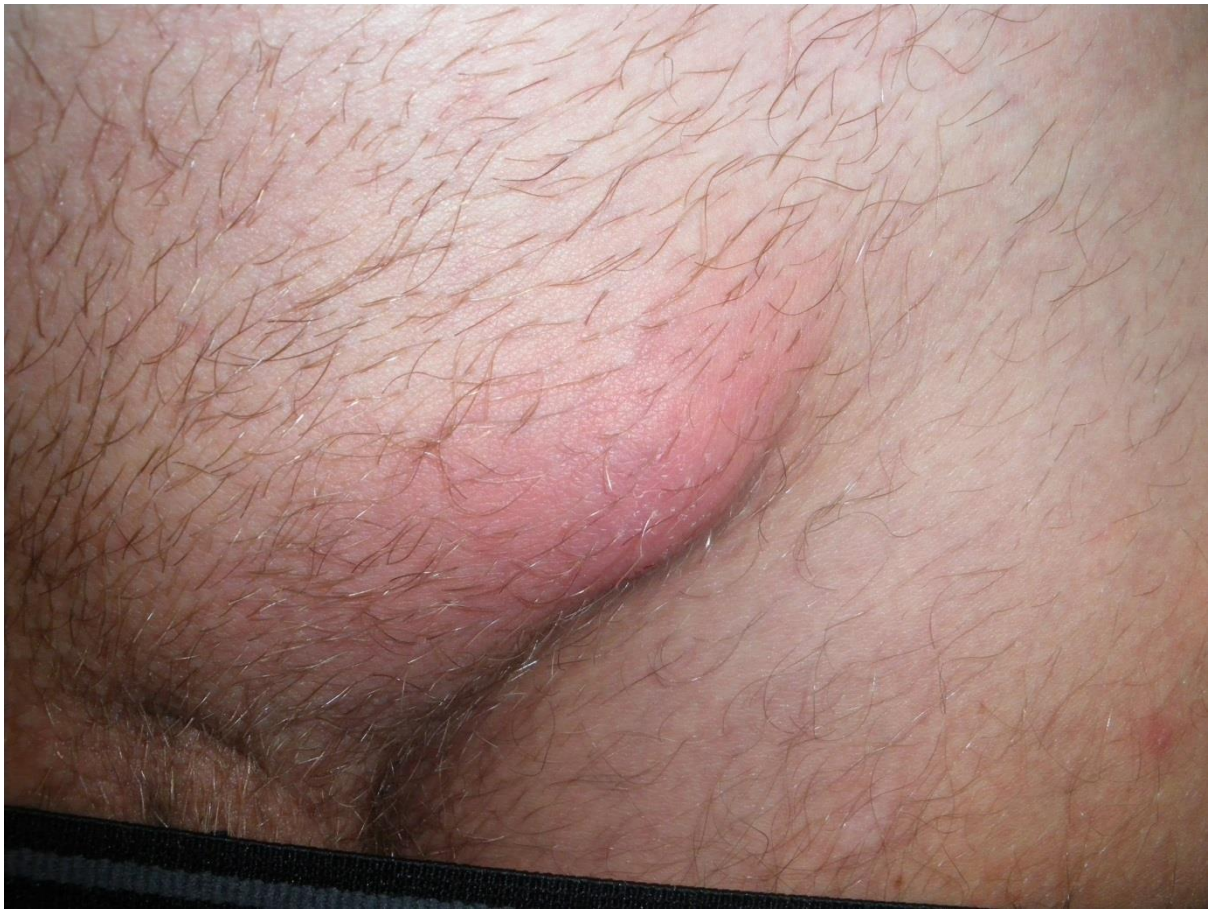

Figure 3: Swelling in the left inguinal region in an HIV positive male

Table 1: General recommendations for specimen types for chlamydia screening in asymptomatic individuals*

	Women	Heterosexual men	Men who have sex with men
Routine specimens	First pass urine[#] or vaginal swab	First pass urine	First pass urine, rectal swab and pharyngeal swab
Additional specimens if indicated	Pharyngeal swab and/or rectal swab	Pharyngeal swab	

**Local guidelines and policy regarding recommended specimen type, sites for chlamydia screening, and concurrent testing for other pathogens such as Neisseria gonorrhoeae vary*

[#]Preferred in pregnant women

Table 2: Recommended first line treatment for *Chlamydia trachomatis* infection [61]*

Uncomplicated urogenital chlamydia	Rectal chlamydia	Pregnant women	Pharyngeal chlamydia	LGV
Azithromycin 1g single dose (oral) OR Doxycycline 100mg twice a day for seven days	Azithromycin 1g single dose (oral) OR Doxycycline 100mg twice a day for seven days	Azithromycin 1g single dose (oral)	Azithromycin 1g single dose (oral) OR Doxycycline 100mg twice a day for seven days	Doxycycline 100mg twice a day for 21 days

**Consult your local guidelines for recommendations for alternative treatments.*