Sexually Transmitted Infections in HIV-Infected Adults and Special Populations

A Clinical Guide

Laura Hinkle Bachmann
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To Kurt, Elisabeth, and Kate, my anchors in this world, and to my patients, for the privilege of working with you and learning from you.

Preface

The synergistic relationship between sexually transmitted infections (STIs) and Human Immunodeficiency Virus (HIV) has been appreciated since early in the HIV epidemic. Transmitted through many of the same behaviors, the co-infection rate of STIs and HIV are significant, particularly in this age when STIs are on the rise again. As of the time of this writing, the most recent CDC STD surveillance (2015) report detailed an all-time high of cases of the three reportable STIs—chlamydia, gonorrhea, and syphilis.[1] While the reasons for these increases are multi-factorial, the promise of HIV Treatment as Prevention (TasP) and the availability of HIV Pre-exposure Prophylaxis (PrEP) likely play a significant role in rising STI rates, particularly amongst men-who-have-sex-with-men (MSM).

New tools and multi-pronged approaches are needed to combat these (often) curable, but frustratingly persistent, pathogens. One important strategy in the fight against STIs and HIV relies on the ability (and willingness) of the physician or Advanced Practice Provider (APP) to include sexual health as part of comprehensive HIV care. This includes taking a competent, nonjudgmental sexual history, performing a physical examination, applying appropriate diagnostic testing and screening strategies and, depending on the situation, sometimes treating the patient empirically. In addition, understanding the nuances of STIs and their interaction with HIV on the molecular, microscopic, and macroscopic level is critical to providing excellent care in the HIV primary care setting. This is not always straightforward. The significant stigma that sexual behavior, and by association STIs and HIV, elicits often presents a significant barrier for both the provider and the patient, compromising care.

While this book does not pretend to have all of the answers, the hope is that this text will aid HIV providers by providing practical information to aid in taking a sexual history and managing the major STI syndromes (as well as the specific STIs) in HIV-infected individuals in an office setting and will serve as a guide for working with special populations around the topics of sexual health. Therefore, the reader will find a mix of practical advice and brief state-of-the-art topic reviews relevant to the HIV provider within these pages.

[1]Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2015. Atlanta: U.S. Department of Health and Human Services; 2016.

I would like to thank each of the outstanding clinicians and scientists who wrote chapters for their generous contribution to this project. This book would not have been possible without their tireless effort—an effort that can only properly be described as a labor of love for their patients and the STI/HIV field. I would also like to thank my family for their patience with this project and their boundless support of me and my work.

I hope that you find this book useful for your practice.

Winston-Salem, NC, USA Laura Hinkle Bachmann

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Part I

Office-Based Approaches to Improve Sexual Health

1 Office-Based STI Management: A Practical Approach to Sexual History Taking and Syndromic Management of Sexually Transmitted Infections

Laura Hinkle Bachmann and Candice Joy McNeil

Introduction

Despite significant progress over the last several decades in the development of diagnostic tests for the evaluation of sexually transmitted infections (STIs), the fact remains that most providers must apply syndromic management skills in order to accurately evaluate STIs in the office setting. There are few point-of-care (POC) tests for the evaluation of STIs at the time of this writing and some older POC tests (i.e., Gram stain, Darkfield) are no longer readily available in the office setting due to increased regulation of laboratory procedures. In order to provide competent syndromic management in the office setting, a thorough sexual history together with a targeted physical examination and an understanding of the etiologic agents associated with common STI syndromes is imperative.

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Sexual History: Let us Start at the Beginning…

The harsh reality is that the prospect of taking a sexual history from a patient is still met with dread by many providers. Much of this may be due to the stigma associated with sexual behavior and, by association, infections transmitted through sexual acts, in our society. As a result, sexual history taking may be the "exception" and not the rule, and many may not see sexual health as a valued part of comprehensive health care. However, studies have shown that patients feel that providers who address sexual history and sexual health concerns are perceived as more competent than providers who skip this important aspect of human health due to limited time and/or downright discomfort with the subject matter [1, 2]. While it may not be necessary to take a thorough sexual history at each clinical encounter, the provider should address this issue at the time of comprehensive health assessment whether it is at a primary care visit or at the baseline visit at entry to human immunodeficiency virus (HIV) care. The latter scenario dictates that a sexual history be addressed at least once a year, even in individuals who report abstinence, as sexual behavior and risk are dynamic. A follow-up sexual history should occur at increased frequency in patients at high risk for STI acquisition (i.e., diagnosed with a curable STI, multiple partners, engaging in drug use, etc.).

The task does not have to be as onerous as it may seem. In fact it is quite the opposite. By

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providing a comfortable, nonjudgmental environment for the patient, providers are likely to learn to appreciate aspects of the patient's life experiences that they were not aware of before, including gaining insight into issues that impact not just sexual health but overall success with HIV care, due to a more thorough elucidation of social and behavioral determinants of health. Also, the sexual history does not, by necessity, need to take a significant amount of time, though obviously the amount of time will vary by the breadth and complexity of the patient's sexual behaviors (and other issues that may be related to sexual behavior such as mental health issues and substance use, etc.).

So where does one start? First, ensuring privacy and confidentiality and making the patient comfortable are all important aspects. For example, it is generally not a good idea to take the sexual history with others in the room (including the patient's partner, friends, or family members), nor to ask these questions of a patient who is already unclothed. Tempting as it may be for busy providers to take shortcuts for the sake of expediency, these pitfalls should be avoided. Several different approaches to determining the specific questions to ask may be considered. For instance, the Centers for Disease Control and Prevention (CDC) recommends the "5 P's" (**P**artners, **P**ractices, **P**rotection from STDs, **P**ast history of STDs, prevention of **P**regnancy) [3]. To expand on this, one may consider adding the discussion of **P**leasure as we know that there is a component of gratification built into the act of sex itself that may influence a patient's practices and use of barrier protection to prevent STIs and pregnancy. The bottom line is that there are common themes for all of these approaches, and they will be reviewed below with a focus on questions that are particularly helpful in the HIV primary care setting.

Setting the Stage

It is important to frame the sexual health questions prior to jumping in by providing context. This does not need to take long and can include a statement such as, "In order to provide the best care, it is important for me to understand aspects of your sexual health. I ask the same questions of all of my patients and your answers will be kept confidential. Do you have any questions before we get started?"

After setting the context, there are a couple of broad questions that providers can put to the patient with subsequent in-depth exploration dependent on the response to the initial key questions (see Table 1.1 for sample questions).

When is the last time that you engaged in any type of sexual activity? It is helpful to keep this question broad and perhaps to emphasize that you are asking about ANY type of sexual activity, keeping in mind that the patient may define sex differently than you do. If the patient states that it has been a long time (keep in mind that the definition of a "long time" may be relative and this should be further clarified), the provider does not need to pursue additional information for the sake of guiding STI screening; however, all individuals should have baseline STI screening at entry into care regardless of timeframe of last sexual contact since some STIs can be chronic and may have been acquired months or even years in the past. Following the baseline evaluation, subsequent evaluation should be guided by sexual behavior reported by the patient. In addition, there may be other issues pertinent to sexual health (i.e., sexual dysfunction, depression, etc.) that may need to be discussed in individuals who are not sexually active in order to improve overall sexual health.

How many partners have you had in the last year? In the last 2 months? These questions can help the provider to better understand the patient's risk for STIs. It can also be helpful, during follow-up appointments, to ask about other time intervals (i.e., "since the last time you were here"). In addition, it is important to ask this question periodically even when patients report no recent partners as life circumstances may change and risk can be dynamic. Based on their responses, probing more on relationship dynamics and other contextual factors for risk such as partner concurrency,

Table 1.1 Examples of specific sexual risk questions

When is the last time that you engaged in any type of sexual activity?
How many partners have you had in the last year? In the last 2 months?
When you have sex is it with men, women, or both?
What types of sex do you engage in?
What is the HIV status of your partner(s)?
Do you and your partner use any barrier protection against STIs?
Do you and your partner have sex with anyone else besides each other?
Are you trying to conceive or "father a child"?
Have you been diagnosed with any STIs in the last 12 months (or other logical timeframe)?
Do you have any other questions or concerns?

victimization, substance use, and exchange of sex for resources, may further guide risk/harm reduction strategies [4].

When you have sex is it with men, women, or both? This question should be asked in a matter-of-fact manner and, with practice, will roll off of your tongue. It can be helpful to further clarify the patient's history by asking about sex with transgender individuals (see transgender chapter). It is of utmost importance that sexual orientation is not assumed based on patient phenotype or marital status. While we all know better than to do this, as human beings, it is easy to make assumptions.

What types of sex do you engage in? The primary purpose of this question is to elucidate which anatomic sites should be screened for STIs. An introduction to the question may be something like, "People have all types of sex. In order to take better care of you, it is important that I understand which parts of your body are exposed through sex. This will help to guide the testing that is best for you." It is helpful to clarify simultaneously the directionality of exposure and to define the specifics in a variety of ways. For example, "Does your penis get exposed through sex—meaning are you the insertive partner or 'top'," "Do you practice penile-vaginal sex (or penis in the vagina sex)," "Does your partner perform oral sex on you (or have mouth contact with your vagina/penis)." This is not the time to pull out our Latin-based medical vocabulary and use terms such as "fellatio" and "cunnilingus," for example, as they may be difficult terms for patients to understand and the use of these terms does not always inform the provider about the specific anatomic sites exposed as they do not tease out directionality (particularly for same gender partners). Avoid jargon and use terms and phrases that are easily understood. Though one can consider mirroring the language that your patient is using, you should remain professional. Finally, while detailed study of specific sexual behaviors was not likely part of the training curriculum for most providers, this knowledge can be useful in terms of understanding the risks an individual patient may have for a specific pathogen. It is not uncommon for providers to feel a bit anxious about whether or not they know or understand enough about specific sexual behaviors; however mastering this part of the history taking can provide essential clues in determining STI risk and site specific testing needs. Additionally, by outlining risk-taking behaviors you have the opportunity to provide targeted risk/harm reduction counseling. A (not exhaustive) list of sexual behaviors to consider inquiring about can be found in Table 1.2. For the purposes of this table, activities resulting in penetration and/or significant exposure to body fluids were focused on. It is important for the provider to bear in mind that terms for these behaviors are constantly changing and may vary outside of the U.S. As a rule of thumb, if you encounter a term or behavior that you are not familiar with during the clinical encounter, simply ask the patient to "Tell me more about that…". You will find that patients are often

Table 1.2 Examples of sexual activities

Common terminology	Medical terminology	Definition
Rimming	Anilingus	The act of using the tongue to stimulate the anus
Eat out	Cunilingus	The act of using the tongue to stimulate the clitoris
Fisting		The act of inserting the hand, sometimes gloved, into the vagina or anus of the partner
Fingering		The act of inserting the finger(s) into the vagina or anus of the partner
Blow job	Fellatio	The act of oral stimulation of the penis
Bareback sex		The act of having condomless sex
Felching		The act of extracting/sucking semen from an orifice
Frottage		The act of men rubbing their penises together
Golden showers		The act of urinating on the body or in the mouth of the partner
Sounding		The act of placing various metal instruments into the urethra for sexual stimulation
Top	Insertive anal sex	The insertive or penetrative partner in a sexual act. Often used to describe sexual positioning for men who have sex with men
Bottom	Receptive anal sex	The receptive partner in a sexual act. Often use to describe sexual positioning for men who have sex with men

Sources Caring for lesbian and gay people: a clinical guide; The complete guide to gay men's sexual, physical, and emotional well-being [39, 40]; https://en.wikipedia.org

willing to share this information with their healthcare provider if the question is asked in a genuine and nonjudgmental manner.

What is the HIV status of your partner(s)? Understanding the partner (s) HIV serostatus can inform discussions with the patient as this information may drive decisions around acceptable level of risk and the use of barrier protection for specific acts [5]. This information is also important when counseling patients about the value of a suppressed HIV viral load for transmission prevention as well as to determine if the patient's partner would benefit from HIV pre-exposure prophylaxis (PrEP).

Do you and your partner use any protection against STIs? While patients' should still undergo recommended STI screening regardless of reported condom use, it can be useful to understand whether or not patients use barrier protection and the reasons they may choose not to use these methods. A follow-up question may include, "How often do you use barrier protection with your partner?" If the patient responds, "sometimes," it can be enlightening to determine the driving forces behind that decision with a statement such as: "Help me to understand why you use barrier protection sometimes and other times you don't." The patient's answers to these questions can assist the provider in addressing misconceptions that the patient may have about determining whether or not a partner has an STI, as well as an opportunity to correct any inaccurate understandings of specific behaviors and associated risks. Furthermore, it allows the provider to tailor messages specific to the patient, a key aspect of effective provider-delivered interventions [6–9].

Do you and your partner have sex with anyone else besides each other? This question is geared toward patients who report only one sexual partner, keeping in mind that the risk for STIs is not always directly related to the risk of the patient in front of you but can be impacted significantly by the partner's risk behaviors.

Are you trying to conceive or "father a child"? The appropriateness of this question will be related to the gender of the patient and the partner. However, determining pregnancy intention helps to plan for a healthy pregnancy upfront

Table 1.3 Symptoms associated with specific STI syndromes

Syndrome	Symptoms	Signs	Associated organisms
Urethritis	Discharge, dysuria, "tingling" or pruritus at the urethral meatus	Mucoid, mucopurulent or purulent discharge; enlarged inguinal ± femoral lymph nodes	*Neisseria gonorrhoeae* *Chlamydia trachomatis* *Trichomonas vaginalis*[a] *Mycoplasma genitalium* *Herpes simplex virus* *Ureaplasma urealyticum* (specific serovars) *Neisseria meningitidus* *Adenovirus*
Cervicitis	Abnormal vaginal discharge, bleeding after sex	Cervical mucopus ± cervical friability; ectocervicitis may manifest as petechiae or erosions on the cervix	*Neisseria gonorrhoeae* *Chlamydia trachomatis* *Trichomonas vaginalis*[b] *Mycoplasma genitalium* *Herpes simplex virus* *Ureaplasma urealyticum*
Vaginitis	Abnormal vaginal discharge, abnormal odor, vaginal irritation, vaginal itching, dysuria, particularly external dysuria[c] when significant vaginal/vulvar inflammation is present	Abnormal vaginal discharge, abnormal vaginal pH, vaginal erythema (see pathogen-specific chapters for details)	*Trichomonas vaginalis* *Candida albicans* and other candida species *Gardnerella vaginalis* and other primarily anaerobic bacteria for bacterial vaginosis
Proctitis	Pus or blood on the stools or when wiping, tenesmus, anorectal pain, constipation (sometimes)	Erythema of rectal tissue, purulent discharge, erosions or ulcers (on anoscopic exam)	*Neisseria gonorrhoeae* *Chlamydia trachomatis (including LGV serovars)* *Herpes simplex virus* *T. pallidum*
Proctocolitis	May have proctitis symptoms plus diarrhea and abdominal cramping	As above plus possibly fecal leukocytes	*Campylobacter* sp., *Shigella* sp., *Entamoeba histolytica*, LGV serovars of *Chlamydia trachomatis*, CMV (in very immunosuppressed)
Enteritis	Diarrhea and abdominal cramping	Depending on pathogen possible fecal leukocytes, positive O and P	*Shigella* sp., *Salmonella* sp., *Campylobacter* sp., *Cryptosporidium, Microsporidum, Isospora, Mycobacterium avium intracellulare*
Pelvic inflammatory disease	Abnormal vaginal discharge, lower abdominal pain, bleeding between periods, dyspareunia	Cervical motion tenderness ± pain with palpation of the adnexa ± uterus; Signs of cervicitis may or may not be present	*Neisseria gonorrhoeae, Chlamydia trachomatis, Streptococcus* sp., Anaerobic bacteria
Epididymitis/Orchitis	Swelling and pain of the scrotum/testes	Edema, erythema, and/or tenderness of the testes and epididymis	*STIs (Neisseria gonorrhoeae, Chlamydia trachomatis)* *Enteric pathogens*

(continued)

Table 1.3 (continued)

Syndrome	Symptoms	Signs	Associated organisms
Genital ulcer disease	Ulcers or erosions; single or multiple; diffuse rash; constitutional symptoms may be present	Erosions (single or multiple); bilateral inguinal ± femoral lymphadenopathy	*Herpes simplex virus*
		Single indurated ulcer with clean base, rolled borders, painless; rash on trunk, palms, soles, genitals; bilateral inguinal ± femoral lymphadenopathy	*T. pallidum*
		Multiple ulcers that are painful with dirty base; unilateral (usually) inguinal lymphadenopathy	*H. ducreyi*
		Small papule or ulcer; unilateral (usually) inguinal lymphadenopathy ("the groove sign")	LGV strains of *Chlamydia trachomatis*
Arthritis-dermatitis syndrome	Joint ± skin manifestations in a sexually active adult	Tenosynovitis, polyarthritis, and/or dermatitis	*N. gonorrhoeae*
Reactive arthritis	Antecedent or concurrent infection in the setting of eye, skin, genitourinary, gastrointestinal and/or joint symptoms and findings	Urethritis or cervicitis Dysentery Inflammatory eye disease Mucocutaneous disease	*STIs (N. gonorrhoeae C. trachomatis)* *Enteric pathogens*

[a]More common in men who also have sex with women, in the southern region of the United States and among ethnic/racial minorities [3]
[b]*Trichomonas vaginalis* is associated primarily with an ectocervicitis in women
[c]External dysuria is defined as discomfort after the urine exits the urethra and hits the vaginal tissue versus discomfort within the urethra

(including the prevention of HIV transmission in the context of conception, if applicable) with the ability to optimize outcomes.

Have you been diagnosed with any STIs in the last 12 months (or other logical timeframe)? While a proportion of our patients will have a history of an STI, a history of recent curable STIs (i.e., gonorrhea, syphilis, chlamydia, etc.) will give the provider a clue that the patient should undergo STI screening at that visit and perhaps even more frequently than annually (see relevant chapters for specific recommendations).

Do you have any other questions or concerns? This question can be utilized to wrap things up as well as give the patient an opportunity to bring up an issue that was not directly addressed.

Now that you understand the patient's risk behavior, we will move on to evaluation and management considerations related to common STI syndromes.

Approach to the Patient with Signs and Symptoms of an STI

Prior to the examination, a review of systems (complete or targeted depending on the setting) should be conducted. While most STIs are entirely asymptomatic, an understanding of the

symptoms experienced by the patient in terms of onset, sequence, duration, and specific characteristics can aid the provider in arriving at an appropriate differential diagnosis. See Table 1.3 for symptoms specific to each STI syndrome.

At its most basic, an STI exam should include examination of the mouth, the skin, the lymph nodes (head and neck, axillary, inguinal and femoral), the genitals, and the perianus. Specific signs and symptoms may merit further investigation (i.e., anoscopy).

STIs are generally approached through the use of signs and symptoms that are associated with relatively well-defined etiologic agents and the various STI syndromes will be addressed accordingly below. Of note, the 2015 CDC STD Treatment Guidelines are cited frequently in this chapter. These guidelines are updated at least every 4 years and the reader should ensure that they are utilizing the most recent guidelines for patient care. The most recent guidelines can be found on or linked to the following website: https://www.cdc.gov/std/.

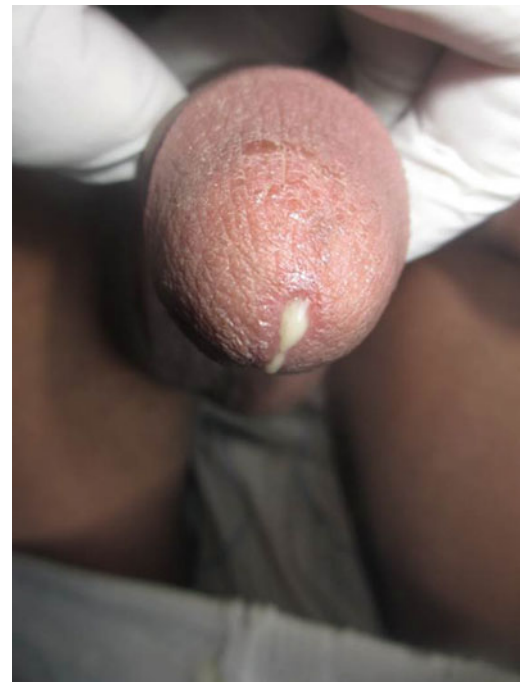

Fig. 1.1 Penile discharge due to *N. gonorrhoeae*

The "Discharges" or "Drips": Recommended Approach

Urethritis

Urethritis can occur in men and in women and is characterized by symptoms ranging from intrameatal pruritus and tingling (in males) to dysuria and frank discharge (Fig. 1.1). The etiologic spectrum of urethritis is broad and can range from bacterial organisms (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium*, various serovars of *Ureaplasma urealyticum*) to parasitic (*Trichomonas vaginalis*) to viral (*Herpes simplex virus (HSV)* 1 and 2, and adenovirus). A specific pathogen cannot be identified approximately 20–40% of the time, regardless of exhaustive testing [10].

The physical examination is helpful for determining whether or not a spontaneous discharge is present and it can be useful to strip the penis (either the provider or the patient can do this) by compressing the urethra from the base of the penis, moving forward until the glans penis is reached. This maneuver may demonstrate a discharge that may not be immediately evident on exam (and occasionally can produce a discharge in men who deny this sign on review of systems). Examining the urethra with a female patient in the lithotomy position may yield an erythematous urethra on visual inspection and compression of the urethra may elicit a discharge. Additional findings on physical exam that support the clinical impression of urethritis include the presence of inguinal and/or femoral lymphadenopathy (Fig. 1.2). Inspection of the testes and epididymis in men can help rule in (or out) a complicated infection such as orchitis or epididymitis.

Diagnostic Evaluation

Access to Gram stain or Methylene Blue/Gentian Violet (MB/GV) stain to aid in the diagnosis of urethritis is invaluable, though not available in many settings. The Gram stain (or MB/GV) can indicate the presence of inflammation (i.e., ≥ 2 white blood cells/per high power field (hpf) as defined by the 2015

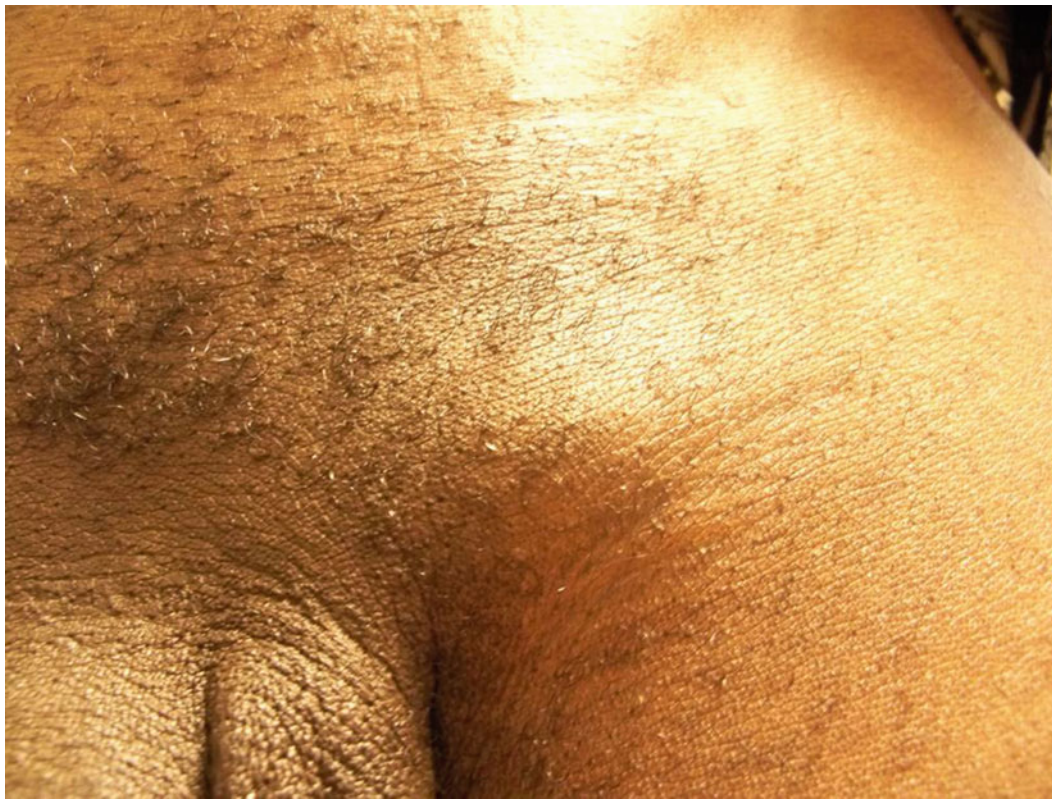

Fig. 1.2 Inguinal lymphadenopathy in a patient with nongonococcal urethritis

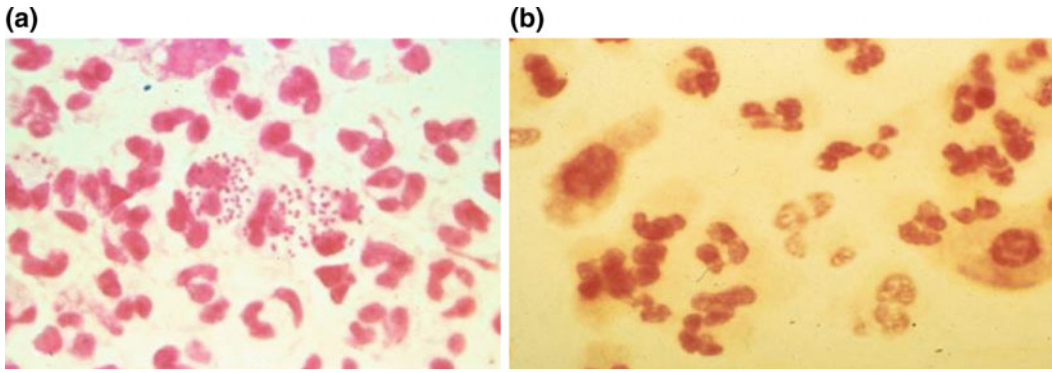

Fig. 1.3 **a** Gonococcal urethritis. **b** Nongonococcal urethritis

CDC STD Treatment Guidelines at the time of this writing; this cut-off will vary in settings in the United States and in other countries) as well as determine whether or not organisms consistent with *N. gonorrhoeae* (intracellular gram negative diplococci or purple diplococci on MB/GV stain) are present (Fig. 1.3) [3]. See Fig. 1.4 for demonstration of penile swab technique. The performance of urethral Gram stain for detecting gonorrhea in men ranges from approximately 50% in asymptomatic men to at least 95% in symptomatic men for sensitivity and the specificity is high [11]. In the absence of an available Gram stain or MB/GV stain, a urine dipstick test

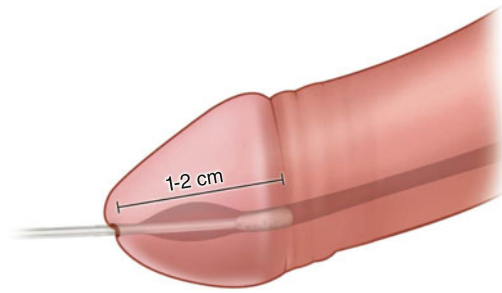

Fig. 1.4 Demonstration of acquisition of penile swab for urethral Gram stain. It is helpful to compress the glans penis in order to open the urethra prior to inserting the swab

that reveals positive leukocyte esterase or a spun urine sediment from first void urine with $\geq$10 WBC/hpf on microscopic exam can lend supportive evidence for urethritis in terms of documentation of inflammation, though these techniques are unable to rule out the presence of gonorrhea, thereby necessitating empiric therapy that covers this organism.

STIs should also be considered in women presenting with signs and symptoms of urethritis. However, women should also be evaluated with a urinalysis and culture in this setting, unless physical examination findings yield another explanation for the urinary tract symptoms. In fact, differentiating between internal dysuria (i.e., pain emanating from inside the urethra commonly associated with frequency and micturia) from external dysuria (discomfort once the urine passes out of the urethra—noticed most prominently when urine hits the vaginal tissues) can be helpful in guiding the thought process related to potential etiologies of the symptoms, as the latter group of symptoms are most common with etiologies that cause tissue inflammation and irritation (i.e., HSV outbreak, severe candida vaginitis, trichomonas, contact dermatitis). Also, suspicion for an STI etiology should be higher for women presenting with urinary tract symptoms who subsequently have negative urine cultures.

Men presenting with urethritis and women in which urethral symptoms are thought to represent an STI (vs. routine urinary tract infection) should undergo testing for *C. trachomatis* and *N. gonorrhoeae* as well as testing for other STIs (i.e., syphilis). Testing for *T. vaginalis* (TV) could be considered in men who have sex with women, particularly in the southeastern part of the United States where TV prevalence in men is higher. HIV-infected women should routinely be tested for TV due to the high prevalence of infection (even in the absence of symptoms) [3]. Further, the detection and treatment of TV, a curable STI in this population, is a point of paramount significance due to potential to decrease genital HIV viral load and shedding with successful elimination of the pathogen [12]. Tests utilizing nucleic acid amplification-based techniques (NAATS) provide the greatest sensitivity, high specificity, and a varied choice of specimen types [12–14] (i.e., urine, vaginal swabs, cervical swabs, etc—see relevant chapter for further detail).

Considerations for Empiric Therapy

Men presenting with symptoms of urethritis and documentation of inflammation based on the procedures above should be treated at the point of care. Unless a Gram stain or MB/GV stain is available to allow the provider to rule out the presence of gonorrhea, empiric therapy should cover both gonorrhea and chlamydia (see relevant chapters for details on treatment options). It is important that providers cover both etiologies in this circumstance, despite the nature of the discharge. While it is true that a purulent, profuse urethral discharge is more consistent with gonorrhea, the nature of discharge is not a definitive distinguishing characteristic. One exception may be an uncommon but particularly flagrant example of the gonococcal discharge that has, somewhat facetiously, been coined the "Bachmann sign"[1] by our group. The sensitivity and specificity of this particular presentation for predicting gonococcal infection has not been systematically studied. If the provider is able to exclude gonococcal infection based on the diagnostic test

[1]The "Bachmann Sign"—a finding where a male patient with a urethral discharge has taken measures to contain or "catch" a profuse discharge. The measures may include toilet tissue stuffed into the underwear (most common in the authors' experience) or something secured to the penis (i.e. an empty M & M® bag, a baby's sock, a condom).

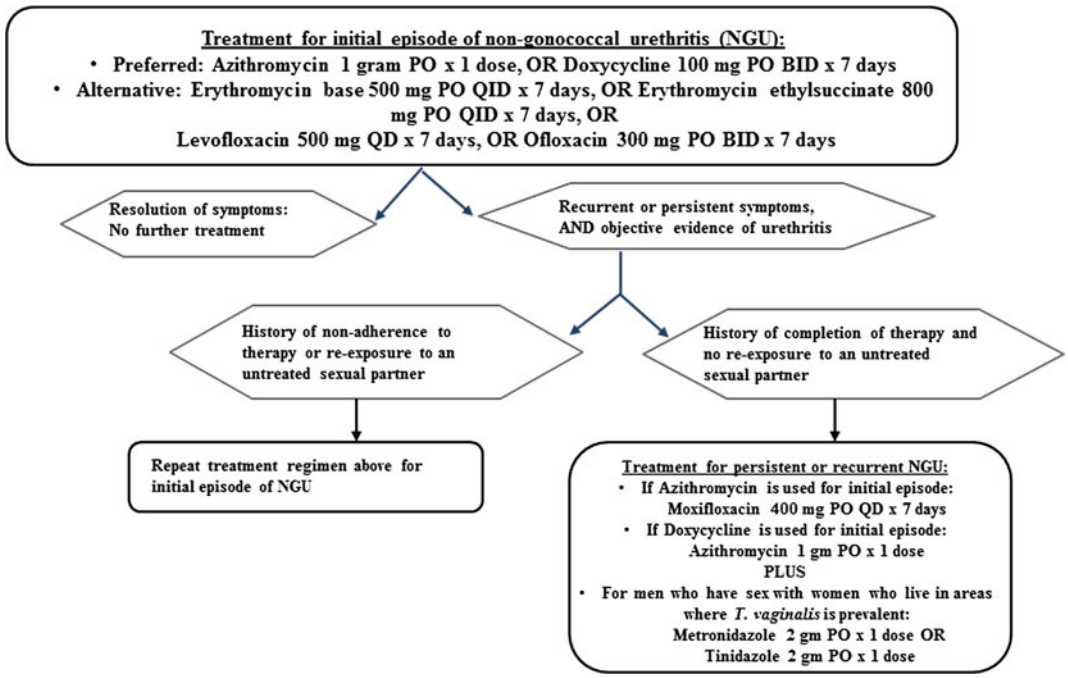

Fig. 1.5 Treatment algorithm for nongonococcal urethritis. Abbreviations: *BID* Twice daily; *PO* Per oral; *QD* Once daily; *QID* 4 times daily. Adapted from Bachmann et al. [10], by permission of Oxford University Press

available, therapy should cover nongonococcal urethritis with either azithromycin 1 g orally once or doxycycline 100 mg orally twice a day for 7 days [3]. If symptoms do not resolve with treatment, reinfection and non-adherence have been excluded, and there is documentation of persistent inflammation on examination (by one of the methods above), the patient would be considered to have persistent urethritis. In this situation, the subsequent course of antimicrobials should cover *M. genitalium* and, (in men who also have sex with women) *T. vaginalis* (Fig. 1.5).

Empiric therapy for female patients presenting with urethral symptoms should be based on examination, results of urinalysis, wet prep, and clinical judgment.

Cervicitis

Cervicitis is defined as inflammation of the cervix and the presence of at least one of two major diagnostic criteria best noted through the "swab test" [3]: (1) the presence of purulent or mucopurulent (i.e., yellow, beige, green) discharge on a white swab used to clean the cervix (Fig. 1.6) and/or (2) the presence of sustained endocervical bleeding following the passage of a small swab into the cervical os (i.e., friability) [3]. Many women with cervicitis are asymptomatic though some women may complain of abnormal vaginal discharge or bleeding between menstrual cycles or after vaginal intercourse. The etiologic spectrum for cervicitis is similar to the etiologies of urethritis in men (i.e., *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium*, *Ureaplasma* sp., *T. vaginalis* and herpes simplex virus with the latter two presenting as more of an ectocervicitis) (Figs. 1.7 and 1.8). Also similar to male urethritis, a significant proportion of cervicitis cases fails to yield a specific pathogen, despite extensive testing [3, 15]. This is especially true in older (>30 years) and lower risk women.

Diagnostic Evaluation

While the presence of leukorrhea on wet prep is supportive of cervicitis (i.e., >10 WBC/hpf on

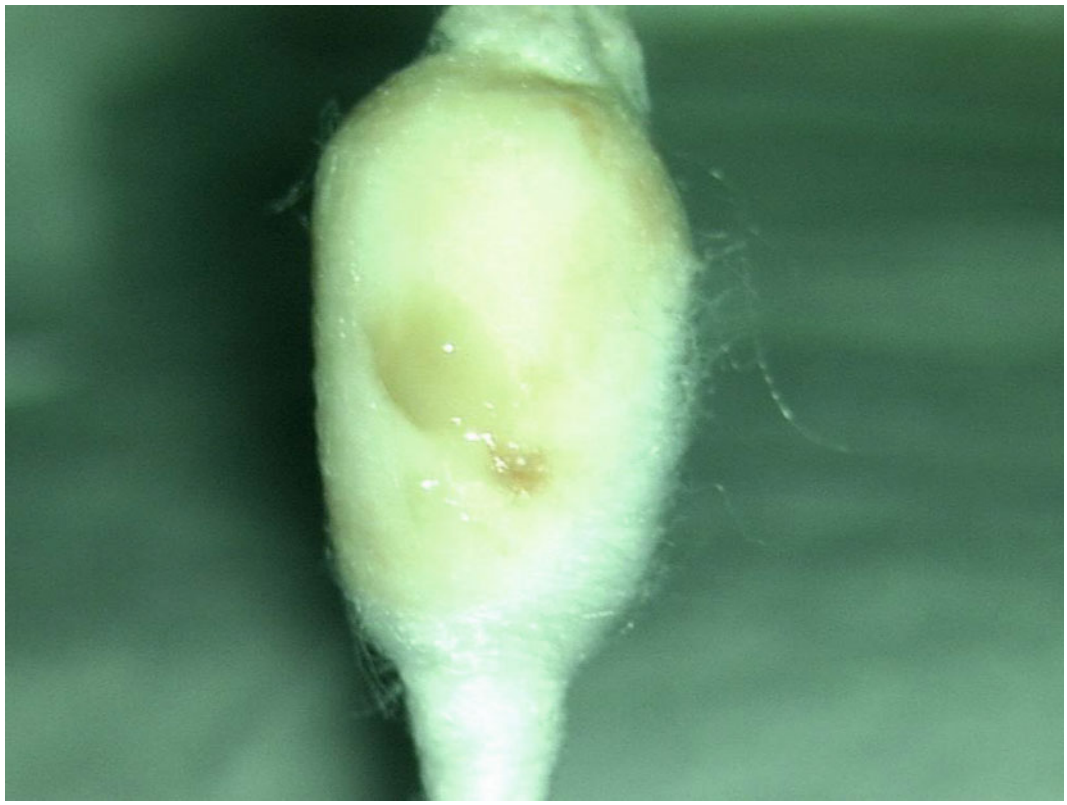

Fig. 1.6 Positive swab test

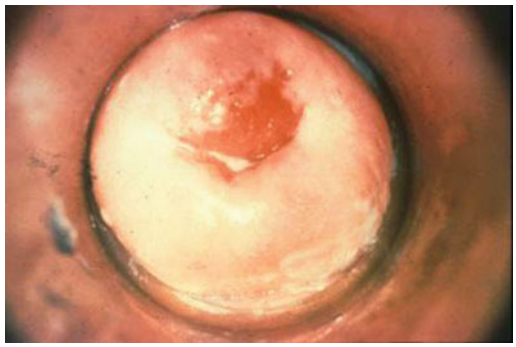

Fig. 1.7 Endocervicitis secondary to *N. gonorrhoeae*

microscopic examination of vaginal secretions), the clinical diagnosis of cervicitis is primarily based on the swab test cited above. Women with cervicitis should be tested for gonorrhea and chlamydia, preferably with a NAATs-based test. Testing for other STIs (trichomonas, syphilis, and HIV, etc.) as well as for bacterial vaginosis (BV) should be performed in women with cervicitis.

Considerations for Empiric Therapy

Decisions about empiric therapy for cervicitis should be based on the patient's sexual risk behaviors and the epidemiology of gonorrhea and chlamydia in your practice. The 2015 CDC STD Prevention Guidelines recommend empiric coverage utilizing a regimen with activity against *C. trachomatis* such as azithromycin 1 g orally once or doxycycline 100 mg orally twice a day for 7 days. Women with cervicitis who are engaging in high risk behavior and/or are from communities with a high prevalence of gonorrhea may merit empiric treatment that also covers gonococcal infection such as ceftriaxone 250 mg intramuscularly once and azithromycin 1 g orally once. Cervicitis noted in low risk

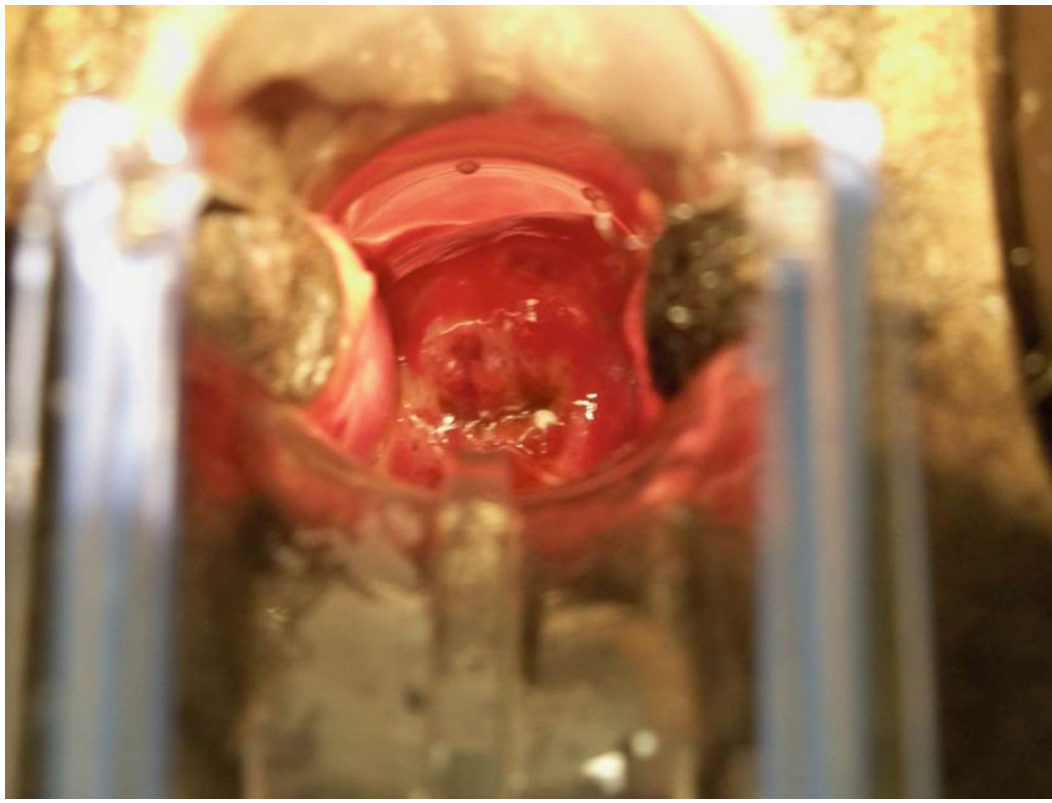

Fig. 1.8 Ectocervicitis due to HSV-2

women who will reliably follow-up does not mandate empiric treatment and therapy can be based on test results.

Vaginitis

Vaginitis is the most common clinical syndrome encountered in women in the HIV care setting. Vaginitis may be associated with abnormal vaginal discharge, irritation, itching, and/or an odor. The most common causes of vaginitis (or vaginosis) include bacterial vaginosis, trichomoniasis and candidal vaginitis though non-infectious etiologies like contact dermatitis, lichen planus, etc., should be considered in certain situations.

Diagnostic Evaluation

Though not relished by patient or provider, the pelvic examination is an invaluable part of the vaginitis evaluation. The external exam, performed prior to the insertion of the speculum, may yield the first clues regarding etiology. Erythema of the vaginal tissues is supportive of a trichomonal or candidal infection and less likely to be consistent with BV (unless a mixed infection is present). In addition to erythema, fissures and satellite lesions may be present in the setting of candida vaginitis (Fig. 1.9). At times, the homogenous adherent vaginal discharge associated with BV may be noted at the introitus during visual inspection. Following the insertion of the speculum, additional details may be noted including the presence and characteristics of the vaginal discharge. The vaginal pH, which should be obtained from the vaginal wall and not the cervicovaginal pool, is helpful in sorting out potential etiologies as candida infection is usually associated with a lower pH (i.e., <4.5) while BV and trichomoniasis are associated with a

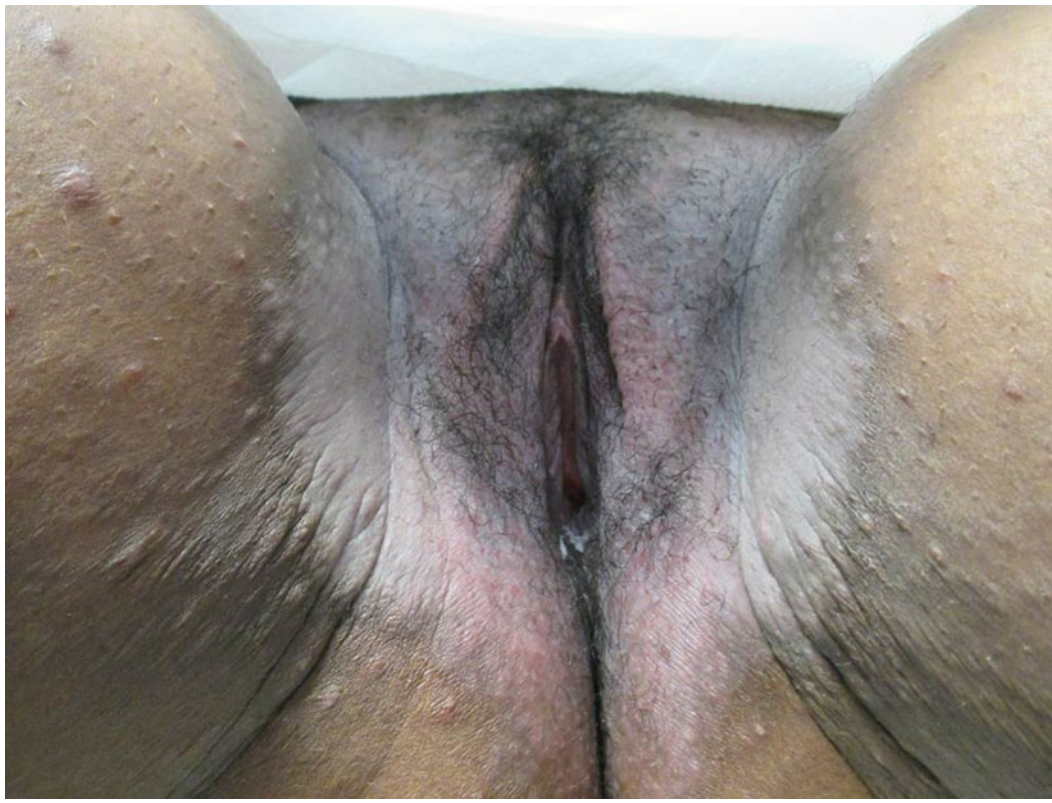

Fig. 1.9 Severe vulvovaginal candidiasis

higher pH. The characteristics of the discharge can be useful as yeast infections are frequently associated with clumpy white to yellow discharge while BV is associated with a homogenous adherent discharge that is usually white/gray. The discharge associated with TV is variable and may present as very profuse and purulent (Fig. 1.10) or even as a normal-appearing discharge. The presence of petechiae on the ectocervix, while not a common finding (present in an estimated 1–2% of women), is highly specific for TV [16].

The wet prep provides additional information including the presence and amount of WBCs (increased WBC being more supportive of candida or TV), clue cells, and trichomonads. The addition of 10% KOH to the tube containing the vaginal swab, or adding a drop of KOH to a slide with vaginal secretions will aid in the detection of the "amine" or fishy odor, otherwise known as the "whiff" test (see Fig. 1.11 for full Amsel criteria) [17]. If adding KOH directly to the tube, it is important that the practitioner has finished reading the wet prep prior as the KOH will destroy the squamous epithelial cells and make subsequent interpretation of the wet prep impossible. The addition of KOH can also be helpful for increasing the sensitivity of the detection of yeast forms (buds and/or pseudohyphae). Several rapid POC tests now exist for the diagnosis of vaginitis with processing times ranging from 10 to 60 min and include the OSOM® BVBLUE® (sialidase) test (Sekisui Diagnostics, Lexington, MA), the OSOM® Trichomonas Rapid Antigen Detection Test (Sekisui Diagnostics, Lexington, MA), and the Affirm™ VP III (Becton-Dickinson, Sparks, Maryland) which can be utilized for the diagnosis of BV, trichomoniasis, and candida infection (see bacterial vaginosis and trichomonas chapter for more detail). Though not a POC test, several

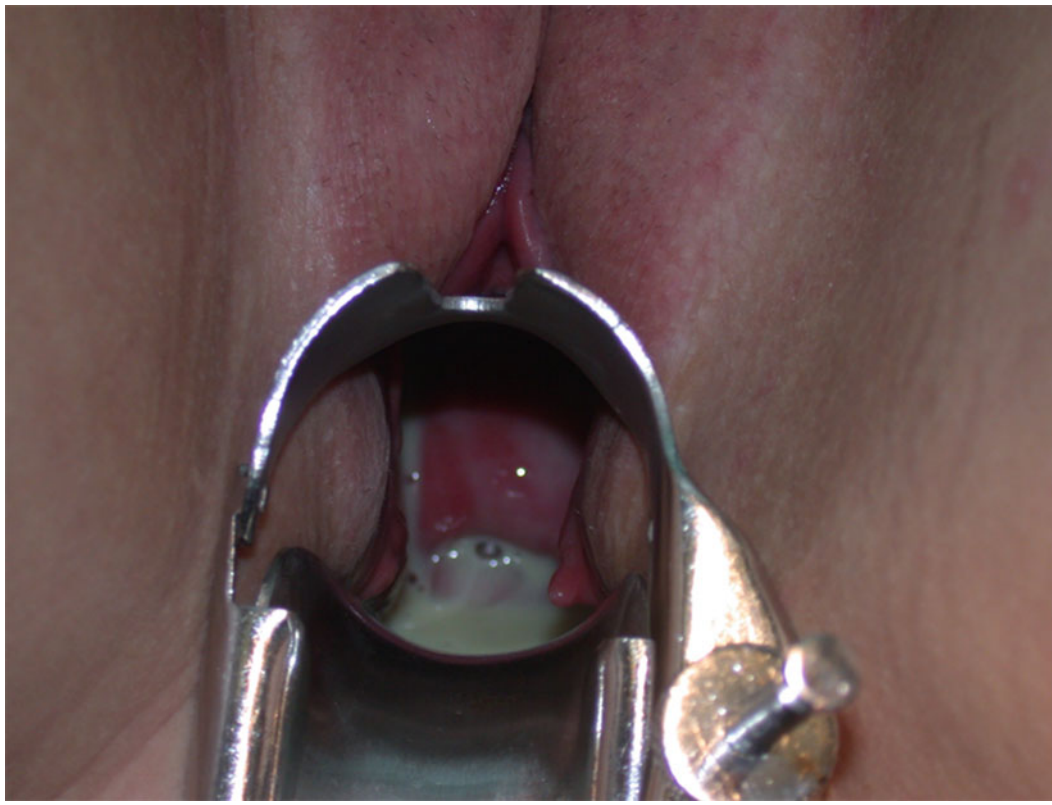

Fig. 1.10 *Trichomonas vaginalis* infection

BV Diagnosis: Amsel Criteria	
Amsel Criteria: Must have at least <u>three</u> of the following findings:	**Vaginal pH >4.5**
	Presence of "clue cells" on wet mount examination
	Positive amine or "whiff" test
	Homogeneous, non-viscous, milky-white discharge adherent to the vaginal walls

Fig. 1.11 Amsel Criteria. *Source* Amsel, Am J Medicine 1983

NAAT-based tests (APTIMA *T. vaginalis* assay (Hologic Gen-Probe, San Diego, CA) and BD ProbeTec^{TM} Q^{x} (BD Diagnostics, Sparks, MD) for *T. vaginalis*) provide additional, highly sensitive, diagnostic options, and can be paired with testing for *N. gonorrhoeae* and *C. trachomatis* on the same swab (if appropriate). Trichomonas culture is also an option in some settings, though this test is less sensitive than NAAT-based tests (see chapter on trichomoniasis).

Considerations for Empiric Therapy

Given the value of the physical exam and the availability of point-of-care tests for vaginitis, the patient can usually leave the clinic with a diagnosis and appropriate treatment. Since the wet prep is less sensitive than culture, the rapid POC tests and NAAT-based testing for TV, sending one of these tests in HIV-infected women with a wet prep negative for TV should be strongly considered since the addition of these more sensitive tests significantly increases the yield [18].

In addition to the infectious etiologies mentioned above, it is important for the provider to keep in mind the noninfectious causes of vaginitis including primary dermatologic processes (i.e., lichen planus) as well as irritant or allergic contact dermatitis. Remember: human beings love to put products on their genitals whether to treat a perceived or real problem or just to enhance the smell. We live in an age of (possibly) unrealistic expectations regarding odors emanating from the genitalia which may lead to excessive cleaning and/or the application of perfumed soaps, lotions, and other products. The tissue in this area is particularly sensitive. Taking a comprehensive history regarding the use of products as well as grooming habits including the frequency of washing and temperature of water (some individuals may actually wash or bathe too often!), whether or not the patient is using irritating cleansers (i.e., bleach, dishwashing detergent, or other caustic substances in the bathtub or directly on the skin), can go a long way in helping the provider determine other offending agents that may be at play (Table 1.4). This is particularly important when the initial workup does not reveal the usual suspects and/or the patient does not respond to therapy. Additionally, examination of the remainder of the skin may be helpful in sorting out primary dermatologic processes such as lichen planus, psoriasis, etc.

Proctitis, Proctocolitis, and Enteritis

Keeping in mind that most rectal infections with gonorrhea and chlamydia are asymptomatic, when patients do present with symptoms of rectal and/or gastrointestinal infection, this should prompt consideration of and workup for sexually transmitted pathogens. Symptoms of proctitis (inflammation of the distal 10–12 cm of the rectum) may include tenesmus, rectal pain, discharge, and/or bleeding. Infection with some pathogens (i.e., lymphogranuloma venereum (LGV)) may result in systemic illness. Proctocolitis, secondary to inflammation 12 cm above the rectum, may present with symptoms similar to proctitis in addition to diarrhea and abdominal cramping. Enteritis usually presents as abdominal cramping and diarrhea in the absence of proctitis symptoms [3]. Each of these syndromes is associated with a spectrum of etiologic agents (see Table 1.3).

Diagnostic Evaluation

Diagnostic evaluation for proctitis should include an anoscopic exam to better examine the rectal mucosa for the presence of erythema, purulent discharge, and/or lesions (Figs. 1.12 and 1.13). Anoscopy also provides the opportunity to collect a specimen for Gram stain to evaluate for polymorphonuclear cells and/or gram negative intracellular diplococci (GNID) if exudate is present. However, gonorrhea should not be ruled out in this setting if not present in Gram stain as this test has low sensitivity for the detection of gonorrhea. Testing should be performed for *N. gonorrhoeae* and *C. trachomatis*, preferably with a NAATs-based test. HIV-infected men with proctitis should be tested for LGV if testing is available (see chlamydia chapter). Testing for HSV (either a NAAT-based test or culture) and syphilis should be performed in all individuals presenting with proctitis. Acknowledging the potential for sexual transmission of enteric

Table 1.4 Common causes of contact dermatitis of the genitals

Type of dermatitis	Chronicity of symptoms	
	Acute	Chronic
Irritant contact dermatitis	Wart treatment medications	Recurrent trauma (i.e., scratching or scraping)
	Caustic cleansing products	Excessive cleansing
		Bodily fluids (i.e., urine, feces, and sweat)
		Yeast infections
		Hygiene products in contact with or applied to the genitals (i.e., douches, lubricants for the vagina, depilatories, liners, and pads)
		Spermicides
		Medications applied topically to the vagina (especially creams)
Allergic contact dermatitis	Medications applied topically to the vagina Spermicides Components of hygiene products applied to or in contact with the genitals Latex-containing products Perfumes	

Source Genital Dermatology Atlas [41]

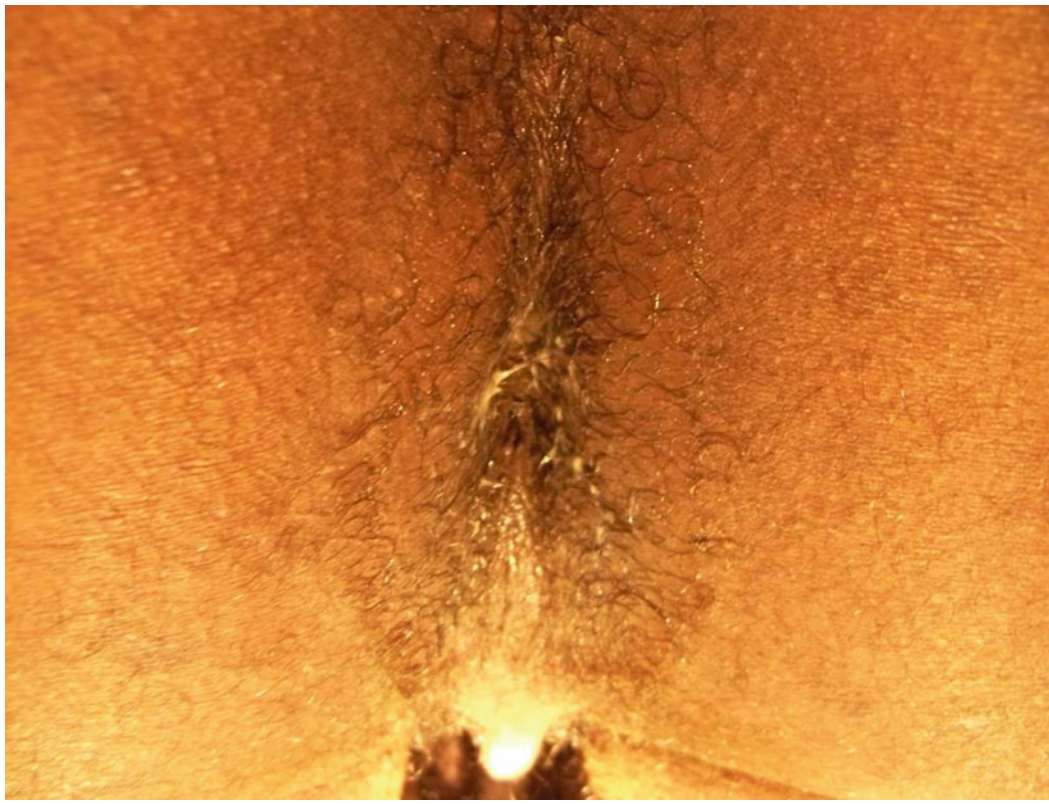

Fig. 1.12 Purulent rectal discharge secondary to proctitis

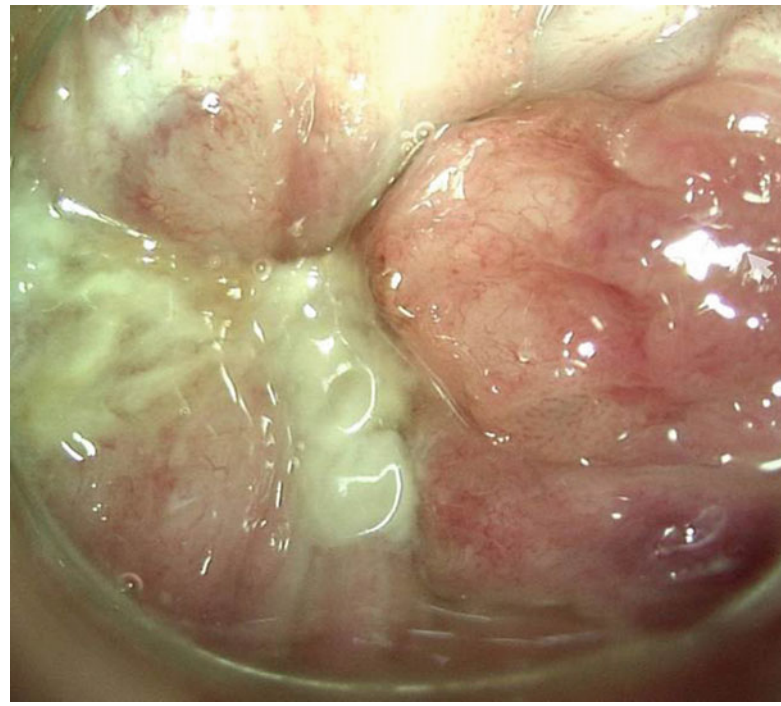

Fig. 1.13 Gonococcal and chlamydial proctitis with purulent exudate noted on anoscopy

pathogens, individuals presenting with symptoms of proctocolitis or enteritis should also have stool examined for the presence of pathogenic bacteria as well as ova and parasites.

Considerations for Empiric Therapy

Patients presenting with symptoms of proctitis should receive empiric therapy to cover both gonococcal and chlamydial infections, even if anoscopy and/or Gram stain is unavailable to confirm the diagnosis. HIV-infected men presenting with these symptoms should, in addition to ceftriaxone 250 mg IM once (and instead of only 7 days of doxycycline), receive doxycycline 100 mg orally twice a day for 21 days to treat potential LGV. If painful ulcers are present in the perianus or intra-anally, empiric therapy should include treatment for HSV (see relevant chapter) [3] (Table 1.5).

Ulcers, Sores, and Rashes: Tips for Evaluation and Management

Genital Ulcer Disease

The etiology of anogenital ulcers may be infectious or noninfectious. The most common infectious cause of genital ulcer disease (GUD) is HSV, followed by syphilis, LGV, and rarely chancroid (*Haemophilus ducreyi*) or granuloma inguinale [19]. As of the time of this writing, the latter two etiologies are exceedingly rare in the United States and most developed countries though they should be considered in individuals from endemic areas.

HSV

Herpes simplex virus classically presents as clustered vesicles, sometimes pustules, which form erosions that may coalesce. HSV can be painful and accompanied by tingling and/or

Table 1.5 CDC-recommended treatments for acute proctitis [3]

Ceftriaxone 250 mg IM × 1
Plus
Doxycycline 100 mg po BID × 7 days[a]
+/- HSV treatment depending on exam findings

[a] MSM with acute proctitis (especially if bloody discharge and/or ulcers are present) and either a positive rectal chlamydia NAAT or HIV infection should be offered presumptive treatment for LGV with doxycycline 100 mg twice daily orally for a total of 3 weeks

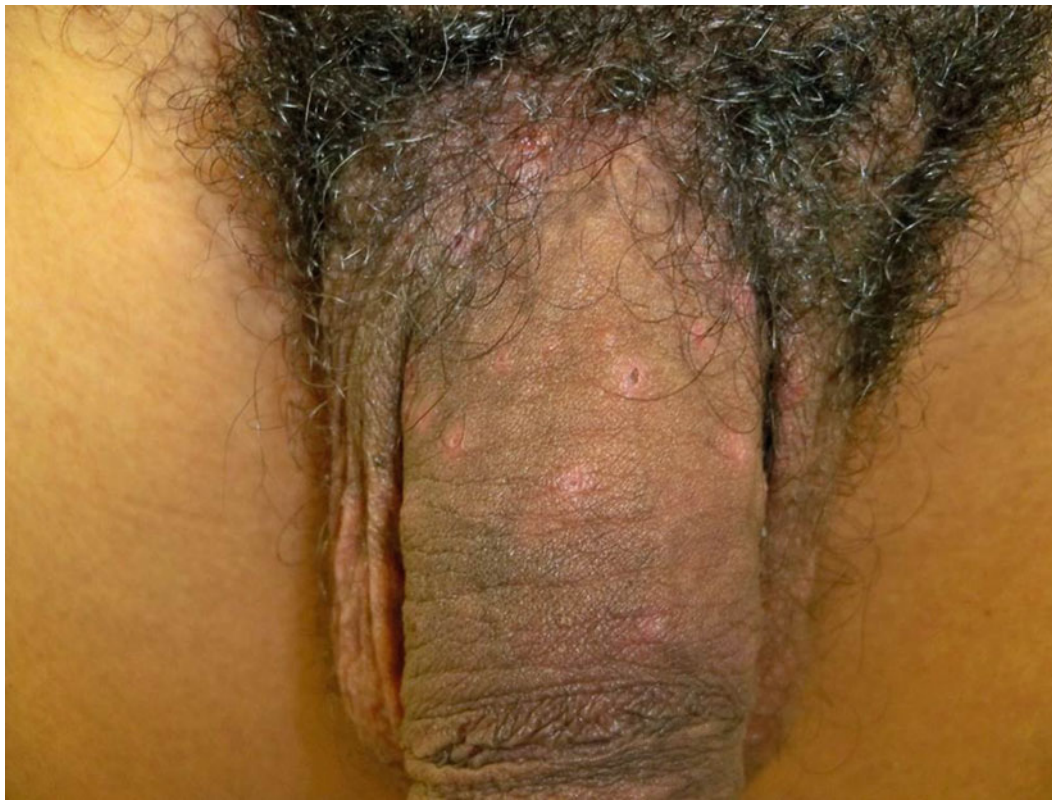

Fig. 1.14 Male patient with primary genital herpes secondary to HSV-1

burning. It is important to keep in mind that, not only are HIV-infected individuals immunocompromised to varying degrees, but also HSV is exceedingly common in this population with prevalence estimates ranging from 60 to 95% [20]. Therefore, uncommon or atypical presentations of HSV will be encountered as part of routine clinical care. HSV can present as a single ulcer that may be painless, as subtle erosions in the gluteal cleft, lesions confused with "hair bumps," or as heaped up lesions with a granulation tissue base (Figs. 1.14, 1.15 and

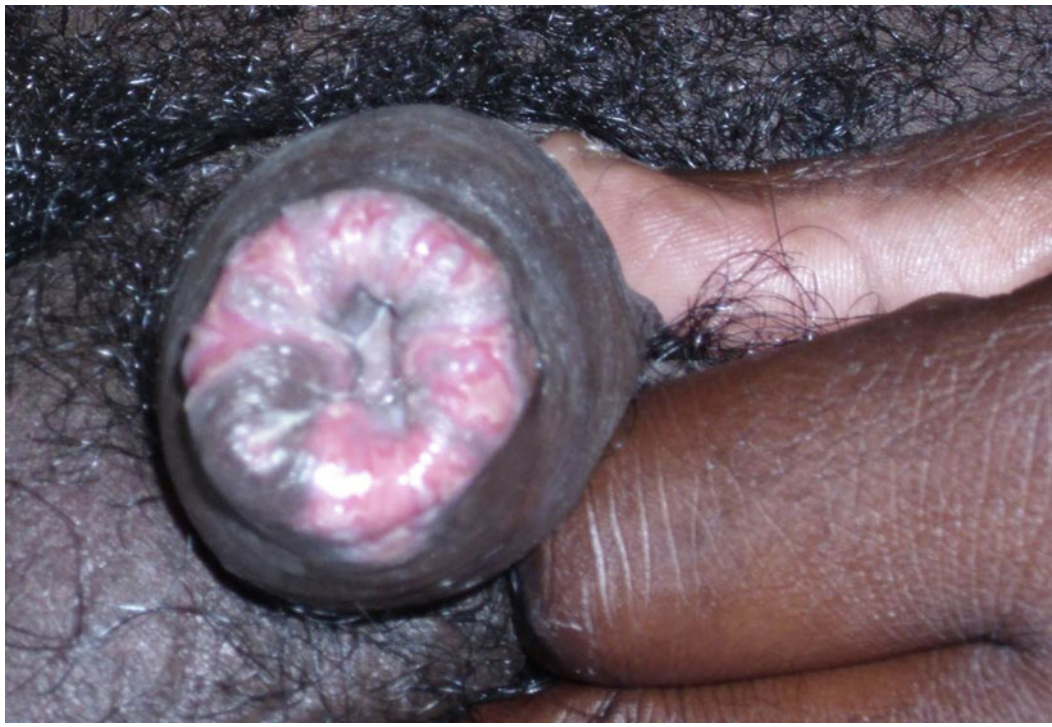

Fig. 1.15 Patient with genital herpes and gonorrhea

1.16). In addition, patients presenting with "recurrent shingles" should be evaluated for HSV.

Syphilis

The classic syphilitic chancre is single and indurated with heaped up/rolled borders and a clean base. Despite these characteristics, syphilitic lesions may not look typical, especially if superinfection or co-infection (i.e., HSV) is present. Occasionally patients present with multiple chancres (Fig. 1.17). Keeping in mind that human beings engage in different types of sexual practices, providers should be cognizant that the syphilitic chancre may present in the mouth (Fig. 1.18), on the cervix, in the anus, or any other body part involved in sexual activity that becomes inoculated with *Treponema pallidum*. While condyloma lata, associated with secondary syphilis, is not ulcerative and perhaps more often confused with condyloma acuminata (HPV), it is important for the provider to be familiar with the appearance of these lesions which may present in the genitals, perianal area, or in the mouth. Condyloma lata is generally not painful but lesions are highly infectious (Fig. 1.19).

LGV

The ulcer associated with LGV is usually subtle, small and painless (Fig. 1.20), and often has disappeared by the time the patient presents with inguinal lymphadenopathy (in the genital/inguinal syndrome). When prominent inguinal lymphadenopathy is bisected by the inguinal ligament, the classic "groove sign" may be seen (Fig. 1.21) [21]. Perianal and intra-anal ulcers may also be noted with rectal LGV, a form

Fig. 1.16 HIV-infected patient with acyclovir and foscarnet resistant genital herpes

that has become more common in the U.S. and developed world over the last decade [21, 22].

Chancroid

The ulcer associated with chancroid typically has ragged, non-indurated borders and a dirty base. Pain is usually present and, while usually singular, multiple ulcers may occur (Fig. 1.22). Chancroid is another cause of the genital/inguinal syndrome and often presents with unilateral lymphadenopathy that may suppurate and drain (Fig. 1.23). Currently in the U. S. cases occur rarely and sporadically [23].

Granuloma Inguinale (Donovanosis)

A rare cause of GUD, Granuloma inguinale is characterized by the development of slowly progressive, painless ulcers. The lesions are often vascular, beefy red, and friable (Fig. 1.24). Regional lymphadenopathy is typically absent. Extra-genital infection can occur with involvement of the pelvis and disseminated infection with involvement of bones, organs and the mouth has been described [3].

Non-STI Considerations

Noninfectious etiologies of GUD include fixed drug eruption, apthae, ulcers from severe contact dermatitis (Fig. 1.25), squamous cell carcinoma, or ulcerative lichen planus. In addition to obtaining history related to the frequency of ulcers, duration, progression (or lack thereof) of the appearance over time, concurrent symptoms, and hygiene habits including all topical products (including products used with sex), a full skin examination can help to narrow the differential diagnosis.

Fig. 1.17 Primary syphilis with multiple chancres

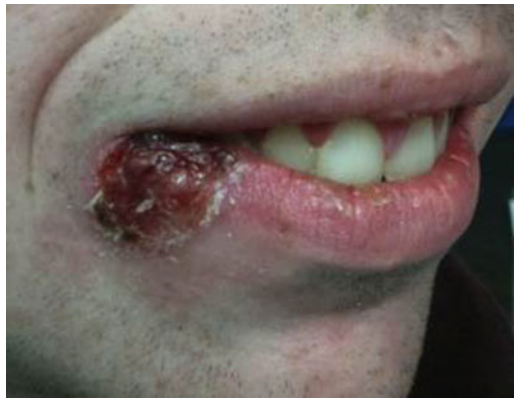

Fig. 1.18 Primary syphilitic chancre

Diagnostic Evaluation

Despite the fact that several forms of GUD are associated with "classic" manifestations, studies have demonstrated that healthcare providers are not good at differentiating etiologies based on the examination alone [24, 25]. In addition, co-infection may be present. Therefore, a GUD evaluation should be comprehensive and include the following: syphilis serology, Darkfield exam or *T. pallidum* PCR (if available); culture or NAAT-based test for HSV and HSV type-specific serology [3]. Atypical ulcers, or ulcers that do not

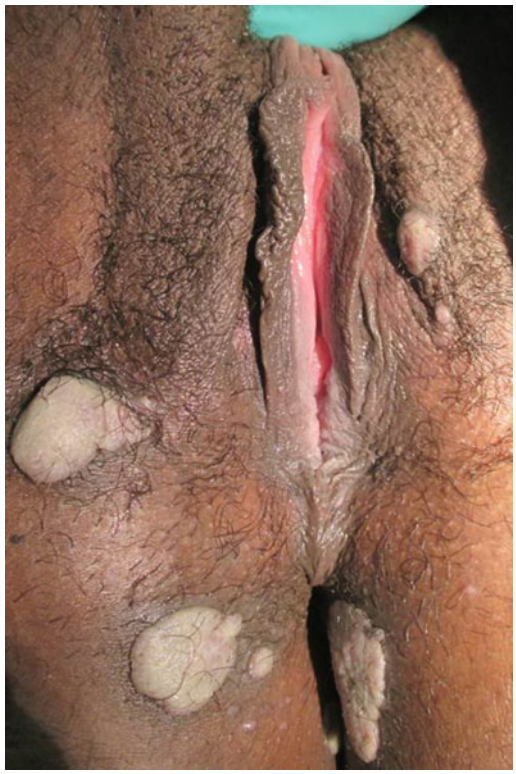

Fig. 1.19 Condyloma lata—may be confused with condyloma acuminata

Fig. 1.20 LGV primary lesion

respond to treatment, should be biopsied. While a STAT RPR (if available) can be helpful, up to 30% of early syphilitic chancres may be associated with a negative RPR [26–28]. Therefore, if clinical suspicion for early syphilis exists, empiric therapy should be started before test results are available, or even in the setting of a negative RPR.

Considerations for Empiric Therapy

Empiric therapy for GUD is largely dependent on the clinical impression. Coverage for HSV may be appropriate, and/or syphilis, depending on the presentation (see relevant chapters for treatment details). A low threshold should exist for empiric syphilis treatment if early disease is suspected, especially among sexually active MSM. Treatment of chancroid could be considered in an individual with one or more painful genital ulcers if the clinical scenario and appearance of the ulcers and inguinal findings are consistent with this entity, if the Darkfield examination and/or syphilis serology is negative and a direct test for HSV (i.e., culture or PCR) is negative. Since not all of these tests will be available at the point-of-care, empiric therapy could be considered if the clinical suspicion is high. CDC-recommended treatments for chancroid include azithromycin 1 g orally once or ceftriaxone 250 mg intramuscularly once or ciprofloxacin 500 mg orally twice a day for 3 days or erythromycin 500 mg orally three times a day for 7 days [3].

Complicated STIs

A Few Words About PID

Pelvic inflammatory disease (or PID) is a dreaded complication in female patients, most frequently associated with gonococcal and/or chlamydial infection. In addition, other organisms (i.e., group B streptococcus, anaerobes) may play a role in this disease process [29]. Women may present with subtle lower abdominal complaints or occasionally more severe symptoms. In addition to lower abdominal pain, symptoms consistent with PID include the presence of an abnormal vaginal discharge, intermenstrual bleeding, and dyspareunia.

Diagnostic Evaluation

When making a diagnosis of PID, it is important to assess the patient's level of risk for an STI-associated infection as well as consider

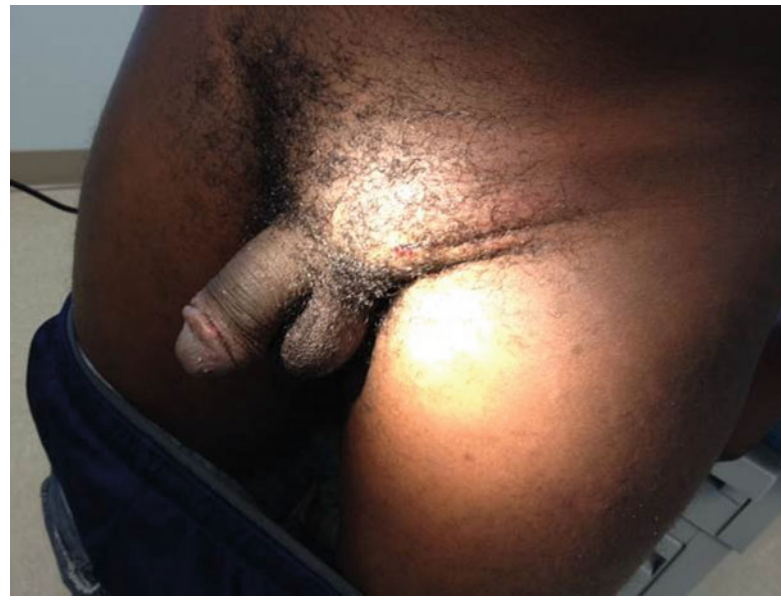

Fig. 1.21 Groove sign

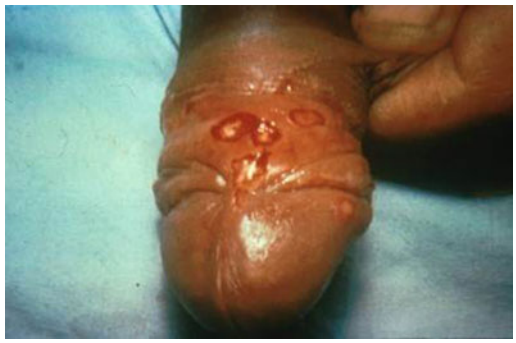

Fig. 1.22 Chancroid ulcers

and potentially rule out other processes such as ectopic pregnancy and appendicitis. Epidemiologic considerations would include age (younger women are more likely to have PID), history of contact with an STI, as well as prevalence of gonorrhea and chlamydia in the patient's community. It can be challenging to make the diagnosis of PID in the office and, in an at-risk individual, the presence of cervical motion tenderness, uterine tenderness and/or adnexal tenderness on bimanual exam should prompt consideration of this diagnosis. Additional tests that strengthen the probability of a PID diagnosis

Fig. 1.23 Regional adenopathy associated with chancroid

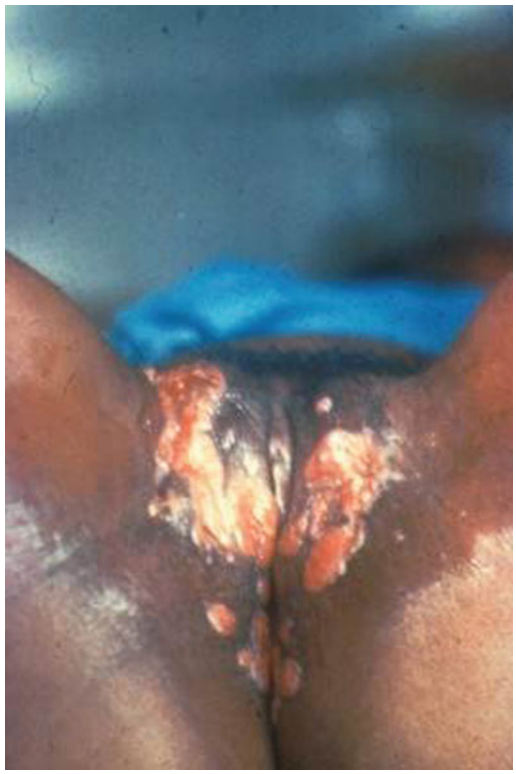

Fig. 1.24 Granuloma inguinale

include the presence of cervicitis, at least moderate white blood cells on the wet prep, fever >101 °C, or a positive gonococcal and/or chlamydia test result. Elevated inflammatory parameters, which are not typically available at the point of care, such as erythrocyte sedimentation rate and C-reactive protein, may also provide supportive evidence of PID [3].

Considerations for Empiric Therapy

Most patients with PID can be treated as an outpatient, as long as they are not toxic, other potential causes of lower abdominal pain are thought to be unlikely or have been ruled out (including the presence of a tubo-ovarian abscess), and the patient can tolerate oral medication. Outpatient regimens recommended by the CDC include ceftriaxone 250 mg intramuscularly once plus doxycycline 100 mg orally twice a day for 14 days ± metronidazole 500 mg orally twice a day for 14 days. Cefoxitin 2 g intramuscularly once plus probenicid 1 gm orally once in addition to doxycycline ± metronidazole as detailed above is another option. The addition of metronidazole should be strongly considered, especially if BV is also present. Patients treated for PID should be rechecked 3–5 days after treatment initiation to ensure that they are improving [3]. If the patient is not improving, other diagnostic considerations should be entertained.

Epididymitis

As briefly mentioned in the text above, the genital examination in the male patient should include evaluation of the testicles and epididymis. Acute epididymitis ($\leq$6 week duration) is often related to a sexually transmitted pathogen, especially in men <35 years of age or men engaging in insertive anal sex [3]. In men >35 years of age, acute epididymitis may be related to a complicated urinary tract infection or procedures related to this system. Clinical presentation of this syndrome is characterized by swelling and tenderness of the epididymis and/or testicle and can vary from subtle swelling of the structure to flagrant, painful, edema that may require inpatient treatment. Typically, unilateral involvement is present (Fig. 1.26). Testicular torsion is the primary diagnosis to exclude quickly as testicular viability is compromised with delayed diagnosis of this condition. Tests utilized to evaluate urethritis would be recommended in the clinical setting of acute epididymitis (see above). Of note, men with epididymitis or epididymo-orchitis may not have an obvious urethral discharge. Urethral Gram stain or MB/GV stain can help to document inflammation that may be subclinical and provide supportive evidence of the diagnosis. Testing for gonococcal and chlamydial infection, preferably

Fig. 1.25 Genital ulcer secondary to severe contact dermatitis from medicated lotion

with a NAAT-based test, should be performed. If there is concern about an enteric pathogen due to a complicated urinary process or participation in insertive anal sex, urine should be collected and sent for urinalysis and culture.

Empiric Therapy

If an STI is suspected as the etiology of epididymitis, the patient should be empirically treated for gonorrhea and chlamydia. For men at risk for STIs in addition to enteric pathogens (i.e., who practice insertive anal sex), intramuscular ceftriaxone in addition to a chlamydia-active quinolone (i.e., levofloxacin or ofloxacin for 10 days) should be considered. Men who are not at risk for an STI, in whom a complicated urinary tract process is far more likely, should receive therapy with a fluoroquinolone (Table 1.6).

Arthritis

Sexually active patients presenting with tenosynovitis, polyarthritis, and/or dermatitis (Fig. 1.27) (arthritis-dermatitis) should be evaluated for disseminated gonorrhea (DGI). Patients with DGI may present with purulent arthritis without rash. Confirmed or suspected DGI warrants an initial inpatient evaluation. Recommended diagnostic testing includes blood cultures (notify lab of concern for gonorrhea as specialized culture techniques will be employed) and site specific STI screening by NAAT or

Fig. 1.26 Epididymo-orchitis

Table 1.6 CDC-recommended treatments for acute epididymitis

For acute epididymitis most likely caused by sexually transmitted chlamydia and gonorrhea:
Ceftriaxone 250 mg IM in a single dose
PLUS
Doxycycline 100 mg orally twice a day for 10 days
For acute epididymitis most likely caused by sexually transmitted chlamydia and gonorrhea and enteric organisms (men who practice insertive anal sex):
Ceftriaxone 250 mg IM in a single dose
PLUS
Levofloxacin 500 mg orally once a day for 10 days
OR
Ofloxacin 300 mg orally twice a day for 10 days
For acute epididymitis most likely caused by enteric organisms:
Levofloxacin 500 mg orally once daily for 10 days
OR
Ofloxacin 300 mg orally twice a day for 10 days

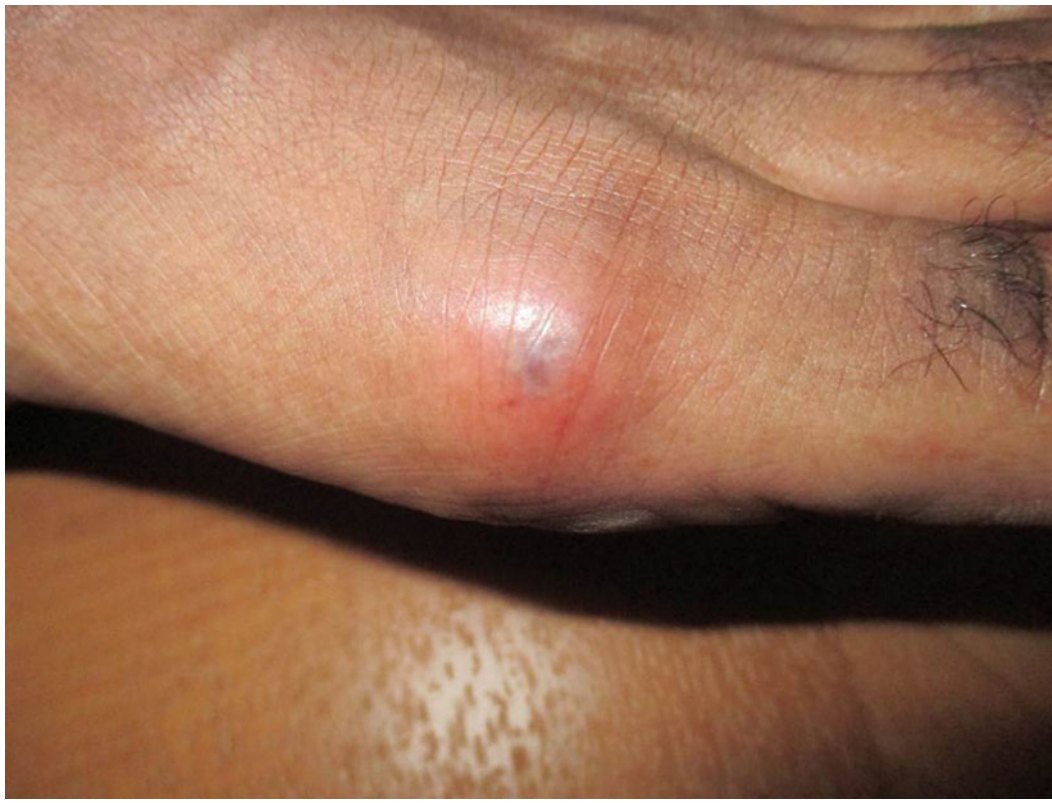

Fig. 1.27 Disseminated gonococcal infection

culture (depending on availability). Diagnostic and therapeutic aspiration of involved joints may also be indicated depending on clinical findings. Initial treatment includes parenteral ceftriaxone 1 g daily and azithromycin 1 g orally in a single dose. Upon defervescence, subsequent coverage consists of an oral cephalosporin regime to complete a 7-day course [3]. Sexually active individuals presenting with eye, genitourinary, skin, and/or joint complaints in the setting of antecedent or concurrent enteric infection or STI, should be evaluated for the possibility of reactive arthritis. Antimicrobial therapy is initiated if the source of the infection is untreated and is often coupled with anti-inflammatory medications.

A Note About Anal Warts

Genital warts are encountered frequently in the HIV primary care setting and, while they can present in a variety of ways, they are usually relatively easy to diagnose (Fig. 1.28). Atypical warts should be biopsied and flat, moist lesions should prompt consideration for possible condyloma lata (and testing for syphilis).

HPV infection is exceedingly common in the human population with over 80% of the general population becoming infected with one or more types in their lifetime [30]. Anal warts do not equal anal sex. For instance, over a quarter of women have anal HPV when tested although a

Fig. 1.28 Examples of genital warts

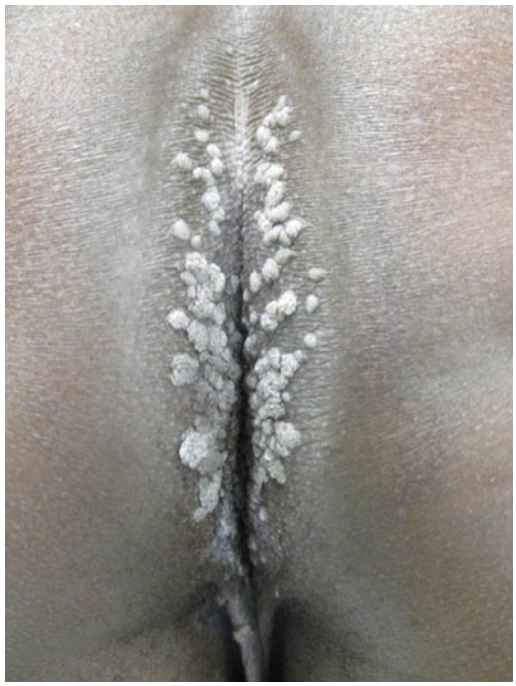

Fig. 1.29 Perianal warts

minority of these women reported anal sex [31]. HPV is spread through close contact and the reality is that sex often involves a variety of activities that could result in anal inoculation of HPV including but not limited to the use of fingers and/or sex toys (Figs. 1.29, 1.30 and 1.31). The bottom line (no pun intended) is that if your patient has anal warts and they deny participating in receptive anal sex, they are not necessarily lying to you!

Treatment

Essentially all of the treatments for genital warts are destructive in nature and none of the current therapies cure the underlying HPV infection, highlighting the importance of HPV vaccination as a primary prevention strategy (see HPV complications chapter). Since a significant proportion of genital warts will spontaneously resolve without treatment, it is not unreasonable to observe the patient if they are willing. However, often patients want to take action and, therefore, many will desire treatment.

A variety of patient and provider-administered therapies are available and, while location and extent of the lesions drive some of the decision-making, the choice of therapy is often based on the provider's comfort with the modality and the patient's ability to purchase topical treatments. (See Table 1.7) for treatments

Table 1.7 Recommended regimens for external anogenital warts[a]

Patient-applied
Imiquimod 3.75 or 5% cream[b]
OR
Podofilox 0.5% solution or gel
OR
Sinecatechins 15% ointment[b]
Provider-administered
Cryotherapy with liquid nitrogen or cryoprobe
OR
Surgical removal either by tangential scissor excision, tangential shave excision, curettage, laser, or electrosurgery
OR
Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80–90%
Solution

Source 2015 CDC STD Treatment Guidelines

[a]Warts involving the urethral meatus, the vagina, and the cervix require additional treatment considerations. See most up-to-date CDC STD Treatment Guidelines

[b]Might weaken condoms and vaginal diaphragms

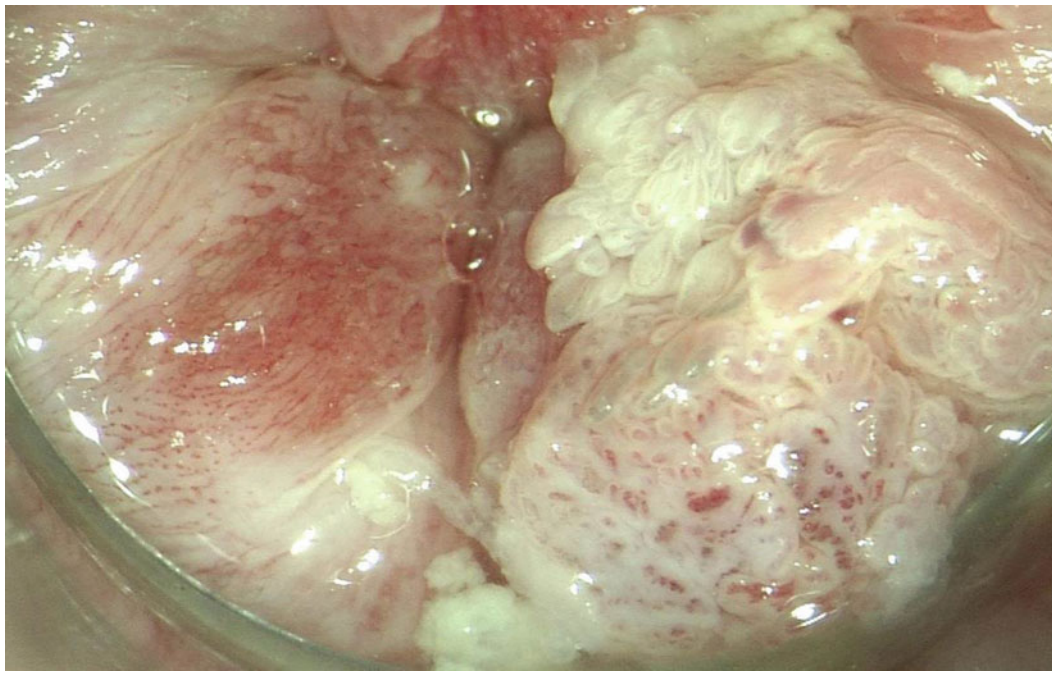

Fig. 1.30 Intra-anal warts

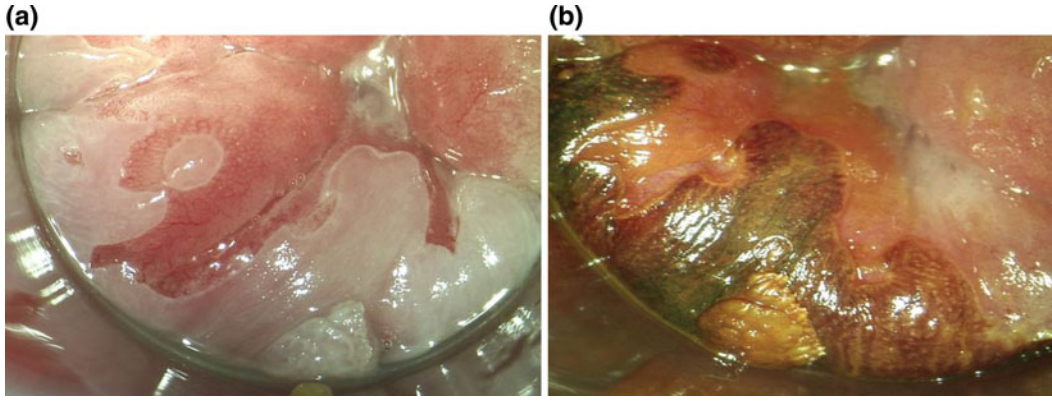

Fig. 1.31 **a** Small intra-anal condyloma (with acetic acid). **b** Small intra-anal condyloma(with Lugol's solution).

recommended in the 2015 CDC STD Treatment Guidelines.

Approaches to STI Screening in the HIV Primary Care Setting

As mentioned earlier, since the majority of STIs are asymptomatic, most patients will not present to the office with a defined set of symptoms that neatly fit into a box consistent with an STI syndrome. Therefore, screening for STIs in the HIV primary care setting is imperative in order to detect asymptomatic infection. The data supporting the dramatic increase in infections detected through the implementation of routine extra-genital infection, particularly in MSM, are extensive and cited throughout this book. For

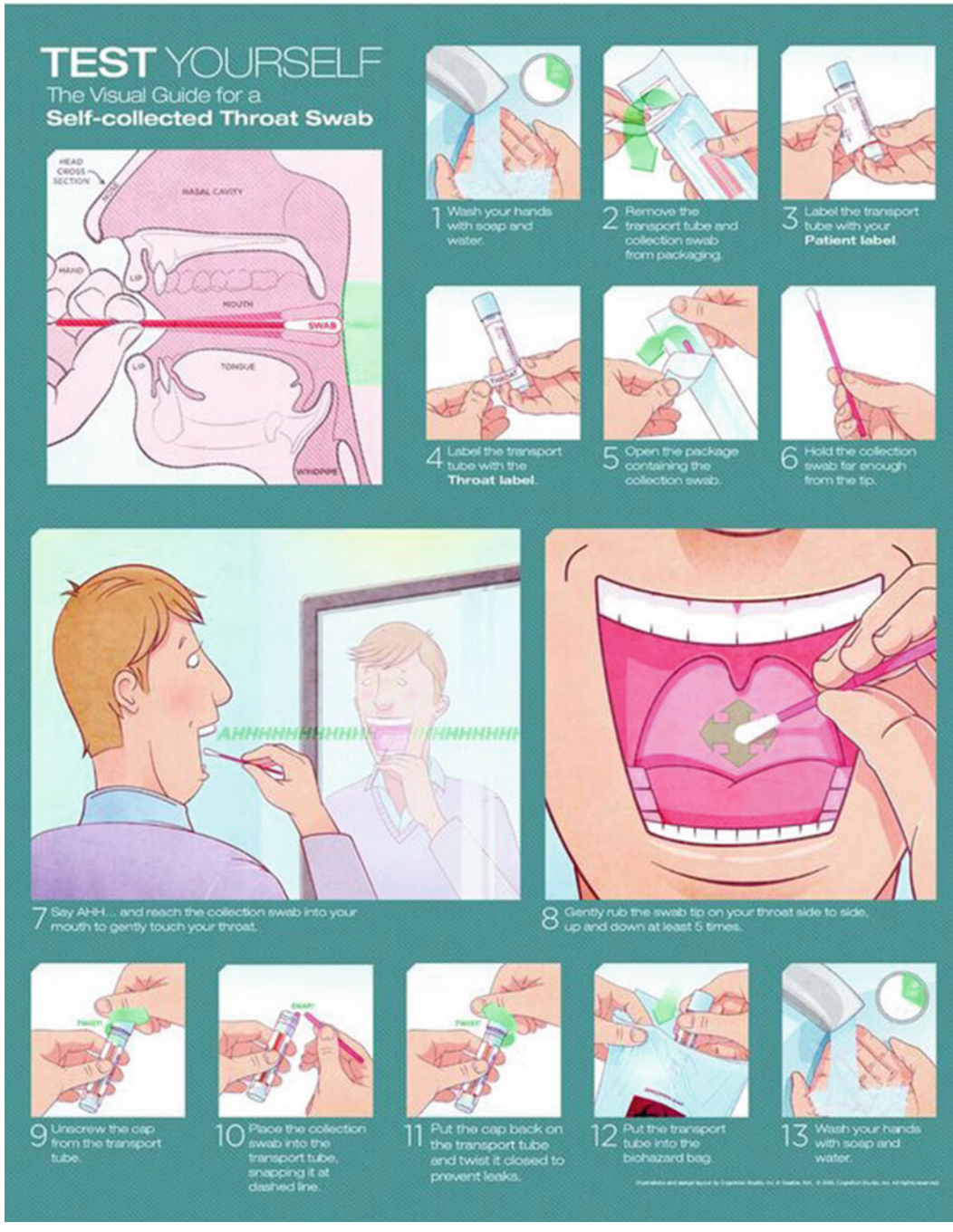

Fig. 1.32 Poster developed to facilitate patient self-collection of an oral swab for STI testing. Printed with permission from Cognition Studio, Inc

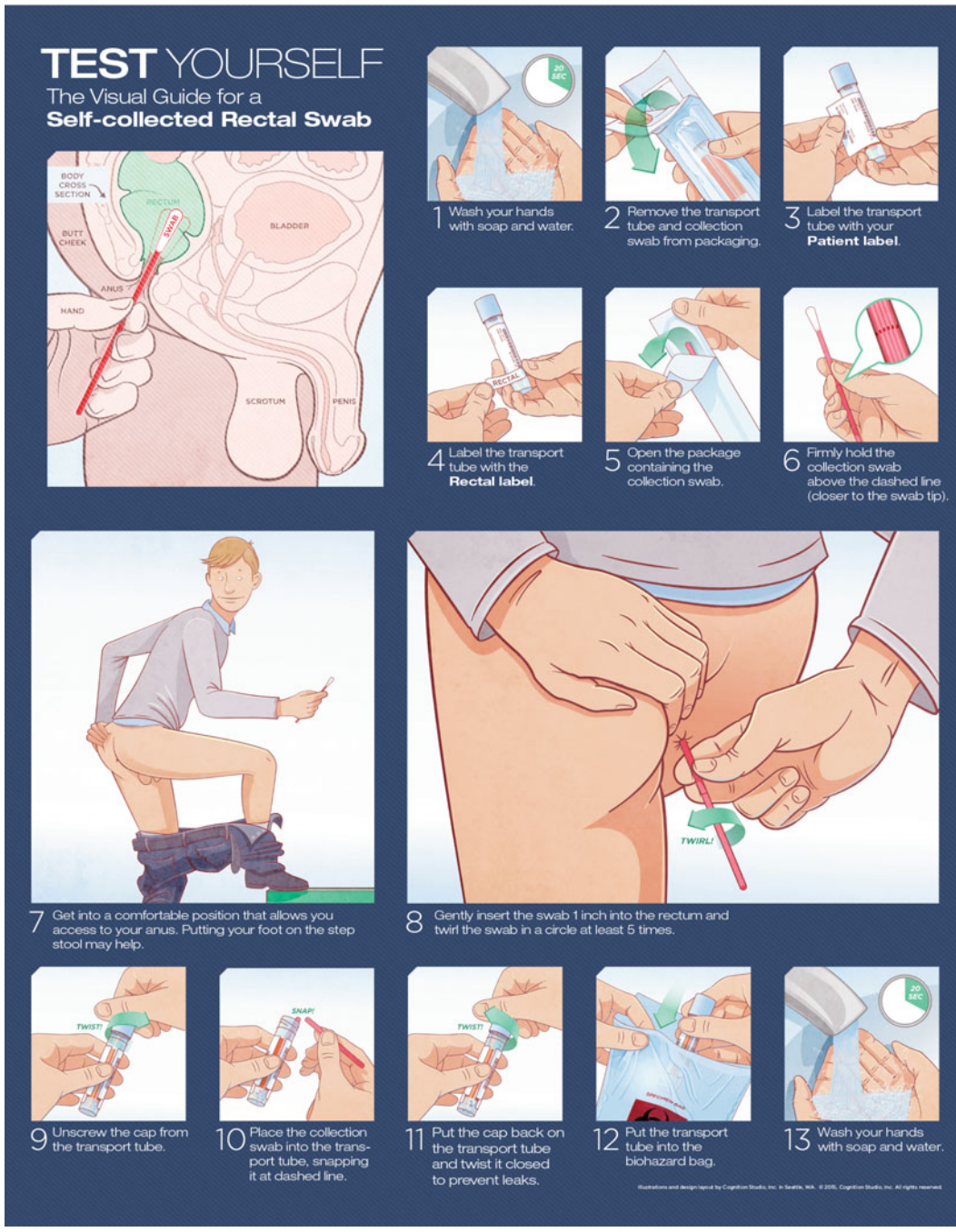

Fig. 1.33 Poster developed to facilitate patient self-collection of a rectal swab for STI testing. Printed with permission from Cognition Studio, Inc

instance, Marcus et al. noted that approximately 84% of gonococcal and chlamydial infections would have been missed with urethral screening alone in asymptomatic MSM who attended a San Francisco STD clinic [32]. While there are screening guidelines published by several distinguished committees [3, 33], the bottom line is that all patients should be screened for syphilis, gonorrhea, and chlamydia at entry to care and at least annually, based on whether or not they are sexually active. Sexually active individuals at increased risk for an STI (i.e., multiple partners, anonymous partners, recent STI, drug use) should be screened with increased frequency, every 3–6 months. Testing for gonococcal and chlamydial infection should be based on site of exposure as oral and rectal infections are more common than urethral infection, particularly in asymptomatic MSM. Women should be screened for *T. vaginalis*. All HIV-infected individuals should be screened for viral hepatitis (and immunized if nonimmune to hepatitis A and/or B) and MSM should be screened annually for hepatitis C [3, 33].

Site specific specimen collection for gonococcal and chlamydia testing can be performed by the provider or the patient, as patient-collected specimens have been shown to perform as well as provider-collected specimens [34–36]. In addition, patient self-collection of STI specimens can be integrated into the HIV primary care environment in a manner that maximizes patient autonomy and decreases the burden on providers. For example, Barbee et al. described their experience with the integration of a patient self-collection procedure into a Seattle-based HIV clinic in which the diagnosis of gonococcal and chlamydial infections increased by approximately 50% and nearly 95% of patients collected their specimens correctly. This program, which utilized a nurse to triage symptomatic patients, a patient self-assessment to guide the patient as to which orifice to swab, and posters to guide patients on the logistics of performing the swab tests (Figs. 1.32 and 1.33), was highly acceptable to patients [37]. The high acceptability of self-obtained collection for testing for oral and rectal gonococcal and chlamydial infection has been documented in other HIV care settings as well [38].

In summary, the ability to take a thorough sexual history and recognize common STI syndromes are important skills for all HIV providers to have in their tool kit. Additionally, the implementation of routine STI screening in the HIV primary care setting is key to detecting asymptomatic STIs. Finally, having the capacity to perform extra-genital testing for gonorrhea and chlamydia, particularly for MSM, is a key component of optimal sexual health services in this setting and several strategies can be utilized including provider collection and/or patient collection methods.

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Behavioral Interventions for Prevention in HIV Care

2

Helen Burnside and Cornelis A. Rietmeijer

Background

The advent of highly active antiretroviral therapy (ART) for the treatment of human immunodeficiency virus (HIV) infection in the mid-1990s leading to dramatic improvements in HIV-related morbidity and mortality, also heralded a fundamental shift in the public health approach of HIV prevention—from the prevention of HIV acquisition among the HIV uninfected that focused on safer sexual and needle use practices, to prevention of ongoing transmission from those infected.

Prior to the ART treatment breakthrough, HIV care had not much to offer beyond management of opportunistic infections and palliative care. At the time, for those at risk for HIV infection, there was little incentive for HIV testing and receiving a dreaded diagnosis, especially when asymptomatic. The prospect of better health outcomes, including for asymptomatic HIV-infected persons with low CD4 counts, changed the attitude towards HIV testing and care, and national programs such as the Serostatus Awareness to Fighting the Epidemic (SAFE) campaign, launched in 2001, actively promoted HIV testing, even among lower risk populations, and linkage to HIV care for those found to be infected [1].

Two subsequent developments have further strengthened this approach. First, a growing body of observational and randomized intervention studies, unequivocally demonstrated the benefits of antiretroviral treatment immediately after HIV diagnosis regardless of level of immunosuppression as measured by CD4 count [2], thus further stimulating early diagnosis and treatment. Second, while it was long thought that HIV viral suppression through the use of ART would reduce the likelihood of HIV transmission, the proof of this concept and the dramatic efficacy of "treatment as prevention" (TasP) was not demonstrated until the results of the HPTN052 study were published in 2011 [3]. A corollary of this fundamental insight were findings from contemporaneous studies showing the efficacy of ART in preventing the acquisition of HIV, a practice now commonly referred to as pre-exposure prophylaxis (PrEP) [4, 5]. Together, PrEP and TasP have revolutionized HIV prevention from a paradigm that was dominated by efforts to change high-risk behaviors, to one that emphasizes the use of antiretroviral treatment for both the prevention of viral acquisition and forward transmission. However, while behavior change interventions benefited the

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prevention of both HIV and non-HIV sexually transmitted infections (STIs) because they targeted behaviors antecedent to both, the shifting focus to the use of antiretrovirals for prevention of acquisition and transmission of HIV, carries the risk of disassociating HIV and STI prevention. Indeed, recent increases in non-HIV STIs, including syphilis, gonorrhea and chlamydia infections, especially among those with concurrent HIV infection [6], must be seen in this context, thus creating special challenges for STI prevention in the HIV care setting.

A Theoretical Perspective

Prior to the prospect of ART as both effective treatment and prevention modalities, HIV prevention efforts during the first two decades of the HIV epidemic were dominated by interventions aimed at changing high-risk behaviors, including reducing number of sex partners and increasing the use of condoms, and for people who injected drugs, avoidance of drug sharing behaviors and use of clean syringes. Behavioral scientists offered numerous theories and models of behavior change to provide a scientific basis for interventions, many of them shown to effectively reduce high-risk behaviors in carefully controlled studies and subsequently packaged for use in the field [7]. A number of these theories will be briefly discussed below, however one, the Health Belief Model [8] is particularly useful in understanding the history of HIV prevention, and the initial overlap with, but also its now threatening divergence from the prevention of other STIs.

The Health Belief Model posits that individuals are more likely to change behavior (e.g., smoking, unprotected sex with multiple partners) to the extent they perceive that this behavior puts them at risk for a certain condition (e.g., cancer, HIV infection); to the extent that they believe that such a condition is detrimental to their health, and finally to the extent that they believe that changing the behavior will mitigate this risk. Clearly, the threat of AIDS as a deadly disease during the early years of the epidemic would favor these beliefs among those at risk. Whether it was the fear of AIDS and/or the effectiveness of behavior change interventions, behaviors did change on a wide scale, resulting in dramatic decreases in STIs, especially among men who have sex with men (MSM), the group hardest hit by the HIV epidemic in the U.S. and Europe. For example, gonorrhea rates among MSM dropped quickly and dramatically in the Denver STD clinic following the initial reports on AIDS as an emerging health crisis [9]. A 12-year trend analysis among MSM at the Denver Metro Health (STD) Clinic between 1982 and 2001 showed a precipitous decline in both gonorrhea and early syphilis among MSM between 1982 and 1988. In 1982, there were 1809 cases of gonorrhea and 138 cases of primary or secondary syphilis, declining to 90 and 20 cases, respectively, in 1988 and 34 cases and 1 case respectively in 1995. Between 1996 and 1999 there were a total of 2 cases of primary or secondary syphilis diagnosed among MSM at the Denver Metro Health Clinic with no cases in 1996 and 1999 [10].

However, the reversal of this trend did not take long to emerge. As ART changed the face of AIDS from an invariably deadly disease to a manageable condition, numerous studies have shown that, as predicted by the Health Belief Model—albeit "in reverse"—a perception of reduced threat was related to increases in both STI (and to a lesser extent also HIV), particularly among MSM [11–15]. In the Denver trend analysis, the increase in gonorrhea among MSM was perceptible in 1996 and nearly doubled from 9% of MSM in 1996 to almost 17% in 2001. However, as nucleic acid amplification tests in those years were not conducted on non-genital specimens (and relying only on gonorrhea culture from the rectum and pharynx), the prevalence of gonorrhea and chlamydia was severely under-ascertained in this group [16]. Most recent data demonstrate that of all MSM visiting the Denver clinic in 2015 ($N = 2008$), 614/1756 (34.9%) HIV uninfected MSM had either gonorrhea or chlamydia at any of the exposed anatomical sites (urethral, rectal, or pharyngeal), compared to 108/224 (48.2%) of MSM with a prior diagnosis of HIV, and 19/28 (67.8%) of MSM with a concurrent HIV diagnosis. Early

syphilis rates were 2.9, 10.3, and 7.1, respectively [17]. The high rates of gonorrhea, chlamydia, and syphilis among persons living with HIV, especially MSM, raise important challenges for the HIV care setting. Clearly, regular screening is critical for early detection and treatment and prevention of transmission of these STIs as has been described in other parts of this book. However, limiting prevention efforts to regular testing may not prevent serious sequelae, for example, ocular syphilis [18], and will not protect against other STIs, including genital herpes and infection with human papillomavirus (HPV), that may have potentially serious consequences, especially among HIV-infected MSM. In addition, other infections, including sexual transmission of hepatitis C are emerging. Thus, in addition to biomedical interventions, including ART and screening and treatment for curable STIs, there will need to be a continued focus on primary prevention and sexual health, especially in the HIV care setting. In addition, behavioral interventions will also be needed to encourage the uptake of and adherence to ART for both clinical and prevention purposes.

In this chapter, we provide a comprehensive review and brief description of behavioral interventions that have been developed specifically for persons living with HIV infection in the HIV care setting. This is followed by a more detailed case study on a training program entitled "Ask, Screen, Intervene" that includes salient components of these interventions and provides a feasible and practical model for integration of behavioral counseling in the provider-patient interaction.

Development of Behavioral Interventions for the HIV Care Settings

Besides the aforementioned Health Belief Model, a number of behavior change theories and models have been useful in the development of behavioral interventions with HIV-positive persons in the HIV care setting. Specifically, the Theory of Reasoned Action [19] and its closely allied Theory of Planned Behavior [20] stress the importance of *intentions* as the psychological entity most proximate to behavioral actions. According to these theories, intentions are influenced by *attitudes* and perceived *social norms*, each in turn influenced by sets of attitudinal and normative *beliefs*. The Theory of Planned Behavior stipulates the additional importance of *perceived behavioral control*, a construct closely allied with *self-efficacy*; the certainty by which one believes one can perform certain behaviors under different and specifically challenging circumstances. This construct, identified in Bandura's Social Cognitive Theory [21], is a singularly important predictor of behavior change. The latter theory additionally suggests that behaviors occur in social context and are often based on behaviors *modeled* by others. Finally, a common concept among these theories is that behavioral changes often are the result of a *decisional balance* where the pro's of changing behavior outweigh the con's or, otherwise formulated, where the positive outcome expectations outweigh the negative ones. Exploring this ambivalence is an important component of motivational interviewing, as we will discuss below.

The Transtheoretical Model [22], specifically addresses the dynamics of behavior change, i.e., that change is a process that transits a number of stages*:* *pre-contemplation* (no intention to change), *contemplation* (long-term intentions), *preparation* (short-term intentions), *action* (actual short-term change, vulnerable to relapse), and *maintenance* (long-term change), where each stage is influenced by different processes. Thus, the behavioral factors described above, attitudes, social norms, self efficacy, and outcome expectations can be thought to play different roles along the transtheoretical change continuum, which has proven to be a useful construct in behavioral interventions [23, 24].

From Theory to Intervention

The previously summarized theories and identified factors influencing behavior change have played a critical role in the development of many

behavioral interventions to reduce risk for HIV and other STIs. A listing of these interventions can be found in the compendium of Risk Reduction Evidence-based Behavioral Interventions (EBI) available at the CDC website [7].

Intervention studies with particular relevance for the HIV care setting are summarized in Table 2.1 [25–32]. These interventions target different behaviors, including safer sex and adherence to antiretroviral medication and employ different intervention modalities, including sessions in individual, group or couples settings. Since one-on-one counseling interventions are most easily implemented in the care setting, we will briefly discuss three intervention studies that have particular relevance for behavioral counseling in the context of the patient/client-clinician interaction.

First, though not included in Table 2.1 because it was not designed for the HIV care setting, Project RESPECT was the first study to demonstrate the efficacy of two brief client-centered counseling sessions in conjunction with HIV testing that resulted in significant reductions in subsequent STIs when compared to standard counseling only providing educational information [33]. The objectives of brief counseling were to assess actual and self-perceived HIV/STI risk, to help the participant recognize barriers to risk reduction, to negotiate an acceptable and achievable risk-reduction plan, and to support patient-initiated behavior change. The first session concluded with a behavioral goal-setting exercise in which the participant arrived at a small risk-reduction step that could be achieved before the second session. At the second session, progress in completing the behavioral step was reviewed, barriers and facilitators to completing the behavioral step were discussed, and a longer-term risk-reduction plan was developed [33]. While the findings from Project RESPECT could not be replicated in a later study [34], most likely due to overall changes in risk perception as a result of the effectiveness of ART for HIV treatment, the insights from this study have had an important influence on the development of behavioral interventions since.

Second, the Options intervention, based on the Information, Motivation, Behavior (IMB) Skills [35] model takes a similar client-centered approach, however, focuses more specifically on intentions and motivational factors driving successful implementation of the behavior change step. Options/Opciones [36] is an individual-level, clinician-delivered HIV risk reduction intervention for HIV-positive persons during their routine clinical care visits and repeated at each visit. The intervention consists of a brief, patient-centered discussion (5–10 min) between clinician and patient at each clinic visit. Based on motivational interviewing techniques, clinicians evaluate sexual and drug-use behaviors of HIV-positive patients, assess the patient's readiness to change risky (or maintain safer) behaviors, and elicit various methods from patients for moving toward change or maintaining safer behaviors. Clinician and patient then negotiate an individually tailored behavior change goal or plan of action, which is written on a prescription pad, for the participant to achieve by the next visit [36, 37].

Third, the Partnership for Health (PfH) intervention, a brief intervention to reduce ongoing high risk behaviors among HIV-infected men and women, specifically stresses the importance of message content, suggesting that negatively "loss" framed messages (e.g., not using condoms will cause me to transmit HIV to my partner) are more effective than positively "gain" framed messages (e.g., condom use will make me stay free from STI) [38].

While these and other counseling interventions vary in details deemed important by their proponents, from the perspective of adaptation, feasibility, and practicability in the busy practice setting, it is useful to stress their similarities. First, client-centeredness implicates that the patient/client is not directed to take certain actions, but rather determines the direction to take and which behavior(s) to focus on. This does not imply that the provider plays a passive role. Rather, the provider initiates the process by eliciting risk information through the use of open-ended questions, by correcting misconceptions and by exploring the patient's ambivalence

Table 2.1 Effective Clinic-Based HIV Prevention Interventions

Reference	Intervention	Target population	Sessions	Format	Main outcome measures
Wingood et al. [25]	Women Involved in Life Learning from Other Women (WiLLOW)	HIV+ sexually active female patients	4	Group	Condom use, incident STIs, psychosocial factors, number of supportive network members.
Description: The WILLOW program consists of 4 4-hour interactive group sessions and is based on the social cognitive theory that emphasizes enhancing knowledge, self-efficacy and skills for safer sex; and the theory of gender and power that addresses how societal expectations of women's role as caregivers constrain the ability to seek new network members, or ask existing network members for support. Small group sessions were conducted over consecutive weeks and implemented by a trained female health educator and co-facilitated by a HIV-positive female peer educator. Sessions addressed medication adherence, nutrition, and provider interaction skills. Over the 12-month period women in the WILLOW intervention, relative to comparison, reported fewer episodes of unprotected vaginal sex, were less likely to report never using condoms, and have a lower incidence of bacterial STIs					
El-Bassel et al. [26]	Project Connect	Heterosexual African American and Latino HIV discordant couples	6	Group	Unprotected sexual acts and protected sexual acts
Description: Project Connect is a couple-oriented prevention model that focuses on couple communication patterns and relationship dynamics to enable women to initiate, and sustain, communication about condom use with long-term intimate partners. Intervention content was theoretically and empirically based on the AIDS Risk Reduction model and the ecological perspective to conceptualize a context- and relationship-specific approach to HIV risk reduction. The intervention consisted of weekly 2-hour sessions, were facilitated by a female facilitator, and included an individual orientation session, and 5 relationship-based sessions. Session content focused on relationship communication, negotiation, and problem-solving skills. Project Connect was the first randomized clinical trail of a relationship based HIV/STI prevention intervention for heterosexual couples and demonstrated that the 6 sessions were efficacious in reducing the number unprotected sexual acts and increased the proportion of protected sexual acts					
Richardson et al. [38]	Partnership for Health (PfH)	Sexually active HIV+ patients in outpatient clinics	Every clinic visit	Individual	Unprotected anal/vaginal sex (UAV) and disclosure of HIV serostatus
Description: The Partnership for Health intervention examined the efficacy of message framing in the context of a brief provider-administered, safer-sex intervention for HIV+ patients in care. The controlled intervention trial took place at 6 HIV clinics: 2 clinics emphasized positive consequences of practicing safer sex, 2 clinics emphasized the negative consequences of unsafe sex, and 2 clinics implemented an intervention to enhance medication adherence. Message framing was tailored to individual risk factors and providers followed a counseling outline, which included a risk assessment, message framing, and identification of a behavioral goal for risk reduction. Among participants who had 2 or more partners at baseline, UAV was reduced by 38% among those who received a loss frame message (almost exclusively MSM) compared with the control arm. Similar results were found for those with casual partners at baseline. No effects were seen in participants with only one partner at baseline and no significant gains were seen in the gain-frame arm. Brief provider counseling emphasizing the negative consequences of unsafe sex can reduce HIV transmission behaviors in HIV + patients presenting with risky behavioral profiles					
Jemmott et al. [28]	Sister to Sister: Respect Yourself! Project Yourself! Because You Are Worth It!	African-American women	1	Individual or Group	Unprotected sexual intercourse, STD positivity rates

(continued)

Table 2.1 (continued)

Description: Sister-to-Sister is a nurse delivered STD/HIV risk reduction intervention that provides African-American women with the information, motivation, and skills necessary to change their behaviors in ways that reduce their risk of contracting HIV or other STIs. This intervention is based on the social cognitive theory and the theory of planned behavior and targets behavioral beliefs about the consequences of protective and risky sexual behaviors. This one-on-one intervention involved a 20-minute session that the facilitator tailored to the specific needs of each participant after conducting an HIV/STI risk assessment interview. The intervention was designed to increase skills regarding condom use. At the 12-month follow-up, participants in the intervention arm reported less unprotected sexual intercourse and were less likely to test positive for an STD then control participants					
Gardner et al. [29]	Antiretroviral Treatment Access Study (ARTAS)	Patients who had received an HIV diagnosis in the past 6 months, not on antiretrovirals, and had not been to a HIV care provider more then once	5 contacts over 90 days	Individual	Attendance at an HIV care clinic at least twice in a 12-month period
Description: ARTAS is a brief case management intervention to link HIV infected persons to HIV care and sustain this linkage for more then a single visit. ARTAS case management is modeled on strengths-based case management, and borrows from theories of empowerment and self-efficacy, which asks patients to identify their strengths and assets and apply these to acquire needed resources. The case manager conducts up to 5 contacts with the patient over 90 days, the contacts consist of building the relationship with the patient, identifying and addressing patient needs and barriers to healthcare, and encouraging or facilitating contact with a medical provider. The ARTAS intervention resulted in a 40% relative increase and a 15% absolute increase in linkage to HIV care at 6 and 12 months. Brief case management is an affordable and effective resource that can be offered to HIV infected patients soon after their diagnosis					
Fisher et al., [30]	Options Project	HIV+ patients	Every clinic visit	Individual	Unprotected insertive and receptive vaginal and anal sex and insertive oral sex
Description: The Options intervention individualizes the clinic visit interaction between the patient and provider to the specific risk dynamics and prevention needs of each patient. The Options intervention is theoretically based on the Information, Motivation, and Behavior (IMB) model and utilizes the collaborative relationship between the patient and provider to assess patient risk behaviors, evaluate patient readiness to practice safer behaviors, strategize steps for reducing/eliminating risk behaviors, and prescribe an agreed upon behavioral goal to reach at the next clinical visit. This intervention is brief, averaging about 5–10 min, demonstrated significant reductions in unprotected insertive and receptive vaginal and anal sex, and insertive oral sex over a follow-up interval of 18 months					
Gardner et al. [31]	Positive STEPS	HIV+ patients	Every clinic visit	Individual	Occurrence of unprotected anal or vaginal sex in the past 3 months
Description: Positive STEPS is a clinic-based intervention and consisted of a 9-question behavioral screener administered to patients by nurses at least once every 3 months, a provider-initiated discussion of safer sex and drug use, a provider-initiated risk reduction plan filed in the patients' medical record, a brochure with prevention messages, and posters in the waiting area, exam rooms, and staff common areas. Medical providers received 4-hour training on the behavioral risk screening tool, targeted counseling, and delivered prevention messages. The intervention demonstration project demonstrated relative risk reductions up to 45% in unprotected anal or vaginal sex in a diverse set of patients from various racial/ethnic backgrounds and sexual orientation					
Gardner et al. [32]	Stay Connected	HIV+ patients	Every clinic visit	Individual	Number of scheduled visits, visits attended, and viral load

(continued)

Table 2.1 (continued)

Description: Stay Connected is a clinic-wide intervention that involves structural changes in the clinic (disseminating brochures to patients, posters in the waiting room and exam rooms, and provider messaging to all patients). Messages delivered on the materials and verbally by clinical providers focused on improved health outcomes for people living with HIV who maintain their HIV care appointments. Overall clinic improvement was 7% for keeping 2 consecutive visits and 3% for the mean proportion of all visits kept (P <0.0001). Larger relative improvement for both outcomes was observed for new or re-engaging patients, young patients, and patients with elevated viral loads

(pros and cons) towards behavior change. Second, behavior change is a step-wise process that takes place along a continuum. While some interventions specifically invoke the transtheoretical stages of change process by actually staging a client for a given behavior to determine what specific action steps are necessary, this is not an explicit part of the RESPECT, Options or PfH models. Nonetheless, knowledge of the transtheoretical model is useful in the process of understanding and interacting with clients. Third, the specificity of the immediate behavioral goals sets the stage for follow-up when the patient/client returns for care. Finally, while this counseling approach should be specific to a given behavior (for example, condom use for anal sex with non-main partners), it can also be applied to other behaviors, including treatment adherence and uptake of HIV pre-exposure prophylaxis.

How to Implement Behavioral Interventions in a Busy Hiv Care Practice

Ask, Screen, Intervene!

The implementation of a provider-initiated, client-centered approach to behavior change is a change process in its own right, where the con's (more time spent with the patient, ambivalence about the effectiveness of the intervention) often seem to out weigh the benefits of a better provider-client interaction. With these dynamics in mind, the National Network of Clinical STD Prevention Training Centers (NNPTC) in collaboration with the AIDS Education and Training Centers (AETC) developed a training program [39] that we will discuss here in some detail as it provides a practical framework for effective STI and HIV prevention in the HIV care setting, named after its three components: Ask, Screen, Intervene (ASI).[1]

Ask

Through the use of open-ended questions, the provider initiates a conversation with the client to explore salient behaviors, including medication adherence, sexual behaviors and substance use. To open the discussion, a "normalizing" statement can be useful, for example: "To provide the best care, I always ask my patients about their sexual activity, so tell me about your sex life." This question can be followed by other open-ended questions, such as "Tell me about your partners," that can then be narrowed to more closed-ended questions that ask about gender and number of partners, new partners, and partners with other partners. A follow-up question would be: "What types of sex have you been having?" (open-ended) with specific questions about oral, anal, and vaginal sex (closed-ended). This leads to an assessment of protective behaviors: e.g., "How do you protect you and your partners during sex?"—with specific questions related to condom use for oral, anal (receptive or insertive) and vaginal sex. Similarly, open-ended questions can also be used to assess substance use, use of clean needles by people who inject drugs, and medication adherence. Throughout the conversation it is important to be non-judgmental,

[1] An ASI Provider Pocket Guide is available at: http://nnptc.org/wp-content/uploads/ASIPCFINAL-1.pdf.

tactful, clear and to re-enforce confidentiality throughout.

Screen

All sexually active HIV-infected clients should be screened for syphilis, gonorrhea, and chlamydia on an annual basis or more frequently based on risk. Specimens for chlamydia and gonorrhea testing should be obtained from all anatomically exposed sites as identified during the "Ask" assessment. Women should be tested for *T. vaginalis* at the initial visit and repeated as indicated by risk. Testing for hepatitis B and C should be done at the first visit and annually if immunity (hepatitis B) or infection is not documented. Further screening recommendations are covered elsewhere in this book.

Intervene

The purpose of this phase is to provide patients with brief, tailored behavioral interventions for risk reduction, comprised of five steps:

1. Discuss risk: Much of this has already been discussed during the "Ask" phase, but the focus here is to explore specific risk behaviors, including unprotected sexual activity, anonymous partners, partners with recent STIs, recreational and intravenous drug use (particularly crystal methamphetamine), exchange of sex for money or drugs, and recent incarceration.
2. Assess and address the patient's knowledge and misconceptions about transmission of HIV/STI, and assess attitudes and beliefs. A question might be: "What are your concerns about giving someone HIV or getting an STI?"
3. Assess circumstances affecting behaviors and assess patient's readiness to change. For example: "How do you tell your partners about your HIV status?" or "What makes it difficult to use condoms with your partners?"
4. The next step is to identify and negotiate a behavioral goal, for example: "What is the one thing you can do to reduce your risk of getting HIV or other STIs?"
5. Finally, the patient is asked to identify a first step toward the behavioral goal that is concrete, incremental, individualized, and realistic. In this phase, motivational interviewing [40] techniques can be particularly useful. For example, with regards to the behavioral goal, patients could be asked (on a scale of 1–10) how important this goal is to them and how likely it is that they will follow through. Next, specifically ask them what it would take to incrementally move the needle on the dial to higher importance or likelihood to change.

In addition to the Ask, Screen and Intervene steps, the ASI model also includes a segment on partner services, especially if the patient has been diagnosed with gonorrhea, chlamydia or syphilis or to bring up the subject of HIV testing and possible pre-exposure prophylaxis for HIV-negative partners. Broaching the subject of partner identification and notification is not always easy, however can be positively framed as follows: "Now that we have talked about ways to keep you healthy, let's talk about ways to keep your partners healthy. How do you feel about telling your partners that they have been exposed to HIV?" Assistance in this process can be obtained from health department disease intervention specialists (DIS) that are trained for the specific purpose of partner elicitation, notification, diagnosis and treatment.

Closing Remarks

In this chapter, we provided a rationale for the continued importance of behavioral assessment and prevention interventions among persons living with HIV and outlined principles of brief patient-oriented counseling that, with appropriate training, can be incorporated in the provider-patient interaction in the HIV care setting. While some clinicians may balk at the idea

that these interventions take more time, a precious commodity in the busy practice setting, many providers welcome the development of a skill set that dovetails well with a more patient-oriented care model where patients and providers share the responsibility for better health outcomes.

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Part II

STI Pathogens and Associated Conditions

Chlamydia trachomatis Infection

3

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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 are the main ways 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 noninfected 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

C. trachomatis are small, nonmotile, 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 noninfective 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 *C. trachomatis* are associated with different types of infections: A–C cause ocular infections ('trachoma'), D–K anogenital infections, and the serovars L1–L3

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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 anogenital 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 polymorphonuclear 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 randomized controlled trials (RCTs) of STI treatment (syphilis, gonorrhea, 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 gonorrhea 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 ninefold 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 (Fig. 3.1). 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

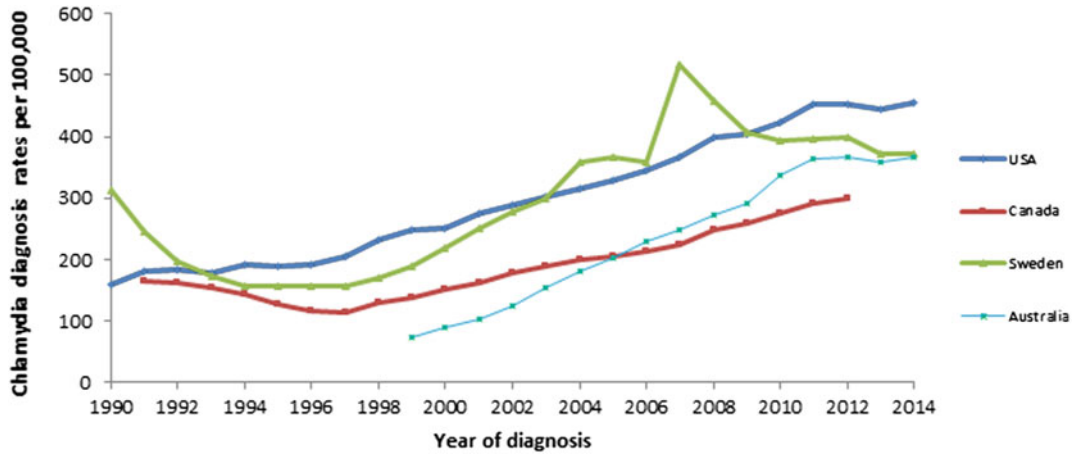

Fig. 3.1 Chlamydia diagnosis rate per 100,000 by year. *Source* USA [28], Canada [129, 130], Sweden [131], Australia [132]

lifetime direct medical costs of $517 million [18].

In high income countries, chlamydia is most common in young heterosexual adults aged $\leq$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 among whom chlamydia positivity has ranged between 2 and 5% for urethral infection and 6–9% 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 STIs 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 gonorrhea, 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 twentieth 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 reemerged 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 behaviors 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 overrepresented in HIV-infected MSM [39], and it remains uncertain to what extent this is biological—reflecting immune suppression—or behavioral 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 noninfected individuals. Cohort studies have shown that if left untreated, most genital chlamydia infections will naturally clear within about 12–14 months on average, but some infections can persist for 2, or even 3 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 6–25%) [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 between 29 and 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 as a result of immune-related pathology with each subsequent infection [47, 57]. Pregnant women infected with chlamydia have an increased risk of preterm delivery [58] and vaginally delivered babies of untreated mothers are at risk of chlamydial conjunctivitis and pneumonitis [59].

Clinical Presentation

There is little evidence to suggest that the clinical presentation of chlamydia infection is different between HIV-infected and noninfected 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 gonorrhea 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 characterized 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 fertilizing capacity and DNA integrity [60, 61].

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. Rectal chlamydia and gonorrhea may coexist 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, edema, and cervical discharge. The cervix may be friable with contact bleeding during endocervical swabbing and the woman may report postcoital 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 [62].

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 two to threefold increase since 1990 [63]. 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, 64], including chlamydial serotypes not associated with LGV. However, LGV is more likely to be symptomatic and may be more clinically severe [65, 66]. 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 [66, 67]. Cases of LGV proctitis can be chronic and present similarly to inflammatory bowel disease leading to misdiagnosis or delayed diagnosis [68]. Asymptomatic rectal LGV also occurs and has accounted for around a quarter of LGV cases in some studies [65, 69]. 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 (Fig. 3.2), the other with increasing swelling in the left inguinal region for one month (Fig. 3.3). A swab was taken from the anal ulcer from one of the men and pus aspirated from the inguinal bubo present in the other. Both specimens

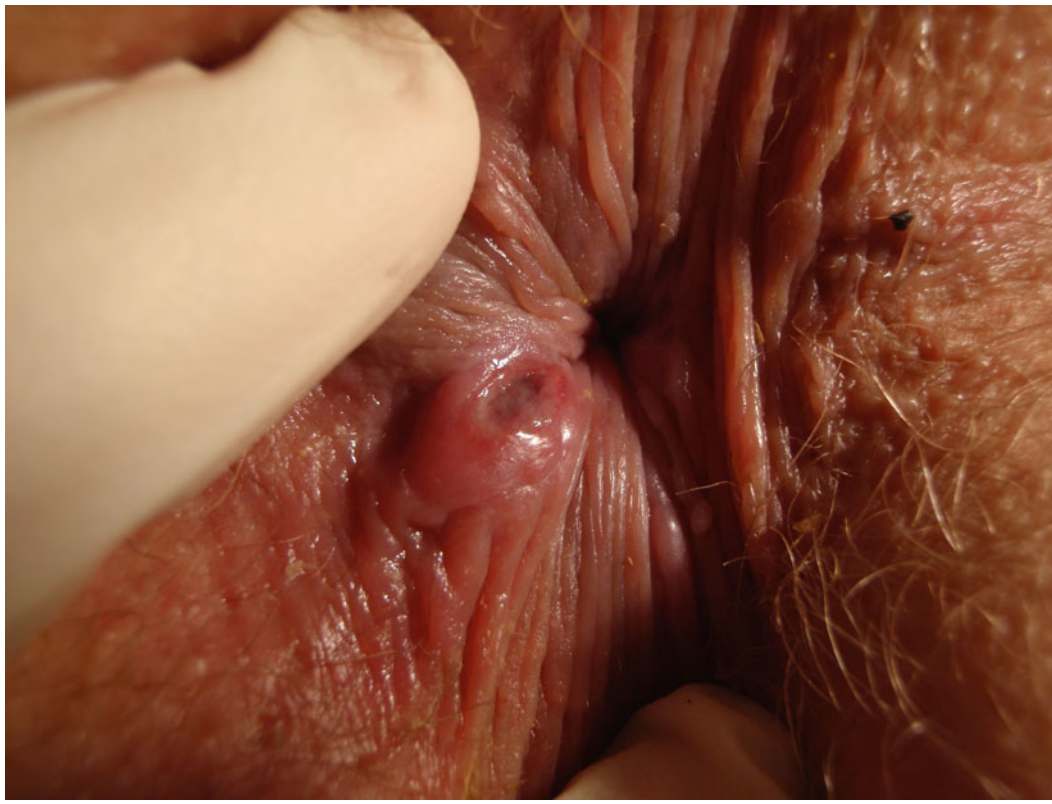

Fig. 3.2 Anal ulcer in an HIV-positive male. Courtesy of Dr. Tim Read

tested positive for *C. 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 100 mg twice daily for 21 days. While the anal ulcer resolved, the inguinal bubo continued to enlarge leading to spontaneous 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 [70–74]. 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) [72]. In England, annual screening is recommended for sexually active men and women under 25 years [73] and in Australia, annual screening is recommended for sexually active men and women aged under 30 years [70]. 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 these groups. Any chlamydia

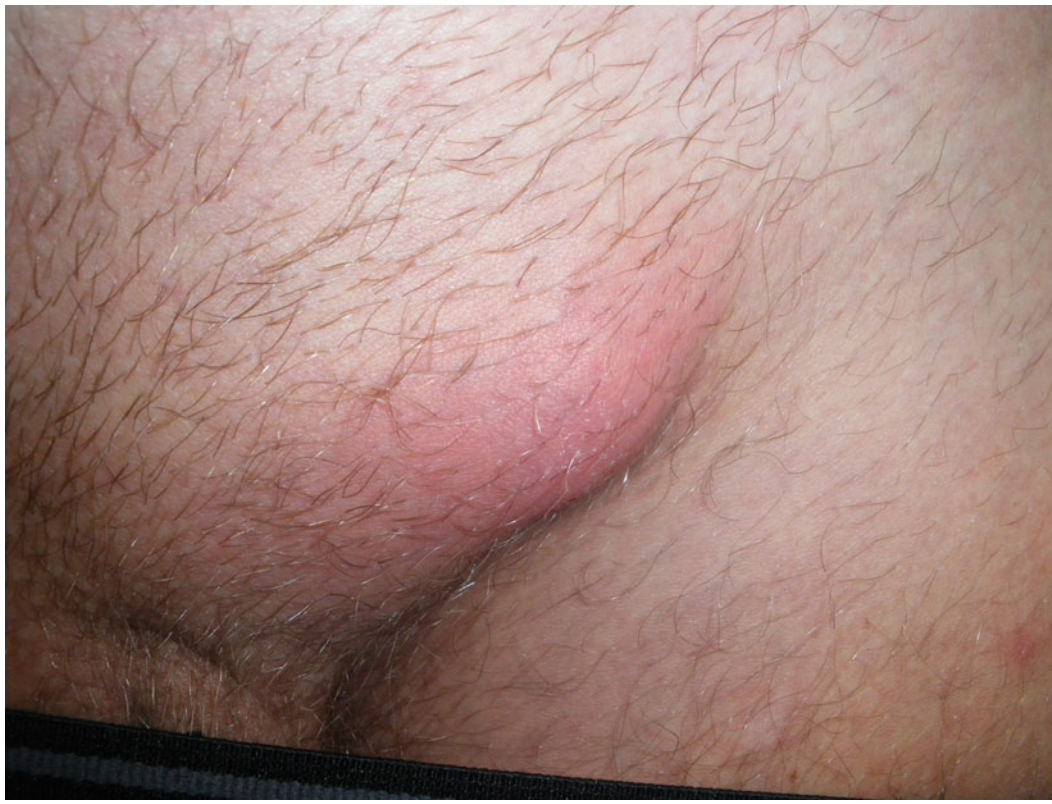

Fig. 3.3 Swelling in the left inguinal region in an HIV-positive male

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 [62, 75]. Screening of MSM should routinely include testing for urethral and rectal chlamydia, with some countries also recommending screening for pharyngeal chlamydia [75].

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 [72]. 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 rescreened 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 [62, 76].

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 can be adopted. For example: "we offer STI screening to HIV-positive patients at least once a year—would you like a check-up?" Framing the opportunity for screening through such an approach may help to normalize STI screening and increase uptake. 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 [77]. Suitably trained nurses are ideally placed to undertake such STI screening [78]. Reminders that prompt STI screening of HIV-infected patients should be tailored and integrated into local medical record systems [79]. 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 [79, 80].

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, reinfection is suspected or the woman is pregnant. A test-of-cure at 3–4 weeks after treatment is still recommended for pregnant women in the United States because of the risk of pregnancy-related complications associated with chlamydia [72], with a second repeat test recommended at 3 months after treatment and/or in the third trimester, depending on timing. In general, 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 [81, 82] that can lead to persistently positive ('false positive') results. Several countries now recommend a test for reinfection for those diagnosed with chlamydia at three months after treatment because of high rates of repeat infection [62, 70]. Among women, a systematic review reported a reinfection rate of up to 32% (median 13.9%), with younger age being associated with higher rates of reinfection [83]. 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% occurring at the 4 month follow up visit [84]. Studies have found that between 5.9 and 28.2% of MSM treated for rectal chlamydia infection presented with a repeat infection on follow-up testing [85–88]. A recent study found no difference in repeat rectal chlamydia infection between HIV-infected and noninfected MSM [89]. Most repeat infections are considered to result from reinfection from an infected partner rather than treatment failure.

Specimens and Diagnostic Assays

Chlamydia infection can be diagnosed in women by testing self-collected vaginal swabs or clinician-collected vaginal or endocervical swabs; first-catch urine may also be used, but can be a less sensitive for chlamydia compared to other specimen types [72]. 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 3.1). NAAT tests that identify *C. trachomatis* specific nucleic acid (DNA or RNA) in clinical specimens are recommended because of their superior test performance [62, 90–92]. Provider-collected and patient self-collected vaginal swab specimens have been found to have equivalent sensitivity and specificity with FDA-approved NAATs [93, 94], and women find self-collected specimens highly acceptable [95]. 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 [96]. However, no manufacturer of chlamydia NAATs has licensed extragenital specimens (rectal or pharyngeal swabs) for diagnosis. Nevertheless, NAATs are still the preferred tests for these specimens and several large commercial labs

Table 3.1 General recommendations for specimen types for chlamydia screening in asymptomatic individuals[a]

	Women	Heterosexual men	Men who have sex with men
Routine specimens	Vaginal swab or cervical swab; first-void urine	First-void urine	First-void urine, rectal swab and pharyngeal swab
Additional specimens if indicated	Pharyngeal swab and/or rectal swab	Pharyngeal swab, Urethral swab instead of urine if indicated for gram stain	

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

have performed the necessary validation studies to allow extragenital NAATs to be used for clinical care [97, 98]. Collecting pharyngeal and rectal specimens should always be considered in MSM and only among heterosexual men and women according to their risk [62, 92].

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 the 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 [99, 100]. 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 [101]. 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 [69]. Genital LGV infection should be considered where chlamydia is detected in MSM presenting with genital ulceration when 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 will often need to be commenced (and completed) 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, although treatment can be initiated at the time of presentation rather than waiting for test results in those partners who have had direct contact with the infected patient. How far back in time to trace

partners and whether epidemiological treatment for chlamydia is offered to individuals reporting contact with chlamydia should be guided by local policy. Partner management for chlamydia is intended to enhance the public health control of chlamydia and also to reduce reinfection 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 STIs. 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 [102]. If this is employed information should be provided to those partners to optimize management including warnings about possible medication side effects, indications for immediate evaluation (i.e., lower abdominal pain in female partners) 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. It is unclear whether treatment efficacy differs by HIV status, as few studies have reported this. A recent RCT comparing azithromycin with doxycycline for the treatment of chlamydia urethritis found no difference in efficacy between HIV-infected and noninfected men, but this was based on a small sample size [103]. STI management guidelines in the US, Europe, and Australia do not differentiate by HIV status for chlamydia treatment [75, 104].

Urogenital Infection

For uncomplicated genital chlamydia infections with non-LGV-associated serovars, azithromycin 1 g as a single dose or doxycycline 100 mg twice daily for 7 days are the most widely recommended treatments (Table 3.2) [62, 92, 105]. 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 [106], and a more recent randomized controlled trial, demonstrated equivalence of azithromycin and doxycycline efficacy [107].

It is important, however, to maximize 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 [62]. Persons treated for chlamydia should be advised to abstain from sexual intercourse for

Table 3.2 Recommended first-line treatment for *Chlamydia trachomatis* infection [62][a]

Uncomplicated urogenital chlamydia	Rectal chlamydia	Pregnant women	Pharyngeal chlamydia	LGV
Azithromycin 1 g single dose (oral) OR Doxycycline 100 mg twice a day for 7 days (oral)	Azithromycin 1 g single dose (oral) OR Doxycycline 100 mg twice a day for 7 days (oral)	Azithromycin 1 g single dose (oral)	Azithromycin 1 g single dose (oral) OR Doxycycline 100 mg twice a day for 7 days (oral)	Doxycycline 100 mg twice a day for 21 days (oral)

[a]Consult your local guidelines for recommendations for alternative treatments

7 days after single dose therapy or until completion of a 7-day regimen and resolution of symptoms (if present) to minimize transmission to sexual partners. To minimize the risk of reinfection, 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 1 g as a single dose or doxycycline 100 mg twice daily for 7 days remain the most widely recommended treatments [62, 92, 105]. 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 [85–88]. While most of these are likely to be due to reinfection, there is concern that a significant proportion may be due to treatment failure [108, 109]. A recent meta-analysis examining rectal chlamydia treatment found a pooled treatment efficacy of approximately 83% for azithromycin 1 g and 99% for doxycycline 100 mg twice daily for 7 days [110]. While these results have raised concerns about the effectiveness of azithromycin 1 g, the quality of evidence included was poor with no RCTs directly comparing azithromycin with doxycycline identified. Therefore, 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 1 g is the recommended treatment for chlamydia infection in pregnant women and has been found to be safe and effective [111]. Doxycycline is contraindicated during pregnancy and therefore is not recommended treatment for chlamydia in pregnant women [111]. Test-of-cure to document chlamydial cure by NAAT within 3–4 weeks after completion of therapy is recommended for pregnant women in some countries [62] because serious sequelae can occur in mothers and neonates if the infection persists [58, 59].

LGV

Guidelines recommend doxycycline 100 mg twice daily for 21 days as first-line therapy for rectal LGV [62, 112, 113], 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, 114–117]. 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 100 mg twice daily for 7 days or azithromycin 1 g single dose which are used for rectal chlamydia may not be adequate for LGV cure, particularly if the LGV infection is clinically severe [114, 118]. This underscores the value of genotyping positive rectal chlamydial specimens in MSM to identify LGV and the need for a longer course of doxycycline in cases of documented or suspected LGV infection. 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 [119–122]. 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 [116].

Antimicrobial Resistance and *Chlamydia trachomatis*

Despite increasing global antimicrobial resistance among other STIs [123], antimicrobial resistance of *C. trachomatis* remains a rare event [124, 125]. Nevertheless, in recent years concerns have been raised over treatment failure in

chlamydia-infected patients treated particularly with azithromycin 1 g single dose [126–128]. Some of these treatment failures can be explained by reinfection, poor compliance or tolerance of treatment, or detection of nucleic acid from nonviable chlamydia due to retesting too early after treatment [108, 109]. However, for some, it is unclear why treatment has failed to clear the infection. This highlights the importance of ensuring that a test for reinfection is conducted at 3–6 months following initial diagnosis and treatment and, if concerns about treatment failure exist, retreatment with doxycycline (unless contraindicated) should be strongly considered.

Conclusion

Chlamydial infections remain one of the most common STIs 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 limit HIV transmission. Clinicians should be aware of LGV, which has reemerged 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 and pregnant women with chlamydia should be treated to prevent mother-to-child transmission of chlamydia and neonatal infection.

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Gonococcal Infections

4

Alex de Voux and Robert D. Kirkcaldy

Introduction

Gonorrhea, a sexually transmitted infection (STI), is one of the oldest known human diseases and has afflicted humans for centuries. Clinical manifestations of gonorrhea in men were described in the Old Testament and medieval European medical texts [1]. The origin of the word gonorrhea (Greek, gonos—"seed", ῥοία—"flow") is attributed to the Greek physician, Galen (AD 129–200), who reportedly ascribed urethral discharge in men to excess semen production. *Clap*, another term for gonorrhea that persists to the present, first appeared in print in 1378, although the origins of the term are disputed. Following the arrival of syphilis in Europe in the late fifteenth century, gonorrhea became mistaken for a stage of syphilis, rather than a separate condition. This confusion was not fully resolved until the identification of the causative organism of gonorrhea by the then 24-year-old dermatovenerologist Albert Neisser in 1879 [2].

Despite its ancient origins and the introduction of effective antimicrobial therapy by the 1930s and 1940s, gonorrhea remains common in the United States and worldwide, including among persons living with HIV/AIDS, and, particularly if untreated, is an important cause of serious reproductive health complications, such as pelvic inflammatory disease and infertility. This chapter explores aspects of gonorrhea relevant to clinical care of HIV-infected adults, including recent basic science findings, epidemiology, clinical presentations, diagnostic considerations, and treatment.

Basic Science

Neisseria gonorrhoeae is an oxidase-positive, gram-negative, encapsulated, obligate intracellular diplococcus, and is an exclusively human pathogen. *N. gonorrhoeae* is fastidious with very specific growth media and environmental requirements, such as the need for CO_2-enriched incubation. With cellular adherence mediated by pili and Opa adherence ligands, the organism preferentially infects columnar or transitional epithelia, such as those found in mucous membranes of the urogenital tract, rectum, pharynx, and conjunctivae [3].

N. gonorrhoeae is able to evade the host-immune response through multiple mechanisms,

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such as surface antigen variation, down-regulation of host T cell and B cell responses, and subversion of the normal function of the complement cascade [3–6]. In addition, *N. gonorrhoeae* appears to influence HIV transmission. Genital gonococcal infections recruit HIV-1 target cells to the site of infection, activate cytokines (TNF-α and Pam3CSK4) and human defensins, and increase toll-like receptor 2 activity (TLR2), heightening one's HIV susceptibility if exposed to HIV through sexual contact [7–12]. For persons with HIV, the presence of gonorrhea is associated with detectable genital tract HIV shedding (Odds ratio 1.8), likely increasing the risk of HIV transmission to a sex partner [13]. Gonorrhea promotes genital tract HIV shedding by recruitment of HIV-infected leukocytes to the genital tract and increased HIV replication owing to inflammatory cytokines [13].

Acute gonococcal infections may have deleterious virological and immunological effects for HIV-infected persons. For those not taking antiretroviral therapy, acute gonococcal infections may increase plasma HIV viral load, reduce CD4 lymphocyte counts, and increase plasma cytokine levels (IL-4, IL-6, and IL-10) [14]. Antiretroviral therapy is likely to mitigate these virological and immunological effects [15]. For women recently infected with HIV and not yet receiving antiretroviral therapy, however, the presence of genital tract inflammation (such as occurs with gonorrhea) may predict higher plasma viral set points and greater CD4 depletion, potentially contributing to accelerated disease progression [16].

Case Illustration

A 25-year-old man presents for routine follow-up HIV care. He denies clinical symptoms and reports adherence to his medications. His most recent CD4 count was 505 cells/mm^3 and viral load was undetectable. Prompted by a quality improvement activity recently initiated by the clinical practice to improve STD screening, his physician notes that the patient was last tested for gonorrhea over four years ago. To guide appropriate screening, his physician asks several questions about recent sexual behavior and learns that the patient is sexually active and has sex with men. The patient has a primary partner, who is HIV-infected and with whom he does not use condoms, and recently has had sex with several other partners, with whom he occasionally used condoms. He recently engaged in condomless insertive anal sex and receptive oral sex; he denies recent receptive anal sex. With the knowledge that the urethra and oropharynx are potentially exposed anatomic sites, the physician collects a urine specimen and an oropharyngeal swab to perform chlamydia and gonorrhea nucleic acid amplification testing (NAAT). Several days later, the test results report the identification of *N. gonorrhoeae* from the pharyngeal swab. The patient is notified of the result and asked to return to the clinic for treatment; fortunately, the clinic recently began stocking injectable antimicrobials to facilitate STI treatment. The patient is treated with dual therapy of ceftriaxone 250 mg as a single intramuscular dose and azithromycin 1 g orally, as recommended by the current Centers for Disease Control and Prevention (CDC) guidance, and is instructed to abstain from sex for 7 days following treatment and until all sex partners are adequately treated. He is advised to return in 3 months for rescreening (or sooner if symptoms occur) and to notify all of his recent sexual partners of their potential exposure to gonorrhea and the need for them to be evaluated and treated. He acknowledges that some of his recent partners were anonymous and he will be unable to locate them, but agrees to notify his primary partner and any other partners that he is able to locate. He is also counseled on risk reduction (reduction in the number of sex partners and correct and consistent use of condoms). At a follow-up visit, he reports that he notified his primary partner and accompanied him to the local sexual health clinic for evaluation and treatment. The patient is rescreened at potentially exposed sites and found to be negative for gonorrhea.

Epidemiology

Approximately, 88 million gonococcal infections are thought to occur annually worldwide [17]. In the United States, gonorrhea is the second most commonly reported notifiable disease: a total of 350,062 cases were reported in the United States in 2014 [18]. However, many infections may be undetected and unreported and CDC estimates that as many as 820,000 gonococcal infections occur annually [19].

Gonorrhea rates in the United States increased sharply in the 1960s and early 1970s, due in large part to demographic changes, shifts in sexual mores, and changes in diagnostic technology (Fig. 4.1). Implementation of a wide-scale gonorrhea screening program in the 1970s and the emergence of HIV/AIDS in the 1980s might have contributed to the subsequent declines. Gonorrhea rates have remained fairly stable since the late 1990s, but reached a historic low in 2009. Since then, rates have increased to a rate of 110.7 per 100,000 in 2014 [18].

Geographically, the South had the highest rate of reported gonorrhea in the United States in 2014 (131.4 cases per 100,000), followed by the Midwest (106.6), West (101.1) and Northeast (84.7) (Fig. 4.2) [18].

The heaviest burden of infection is among those aged 15–24 years [18]. Among both women and men in this category, the highest rates are in those aged 20–24 years (533.7 per 100,000 in women and 485.6 per 100,000 in men in 2014).

The rate among women decreased during 2012–2014 and in 2013, for the first time since 2000, was eclipsed by the rate among men (101.7 in women and 108.7 per 100,000 in men). In contrast, rates in men have increased since 2009, suggestive of increasing cases among gay, bisexual, and other men who have sex with men (collectively referred to as MSM). Increasing case counts among MSM may be due to increasing incidence of infection and/or better detection and increased case finding due to expanded gonorrhea screening at nongenital

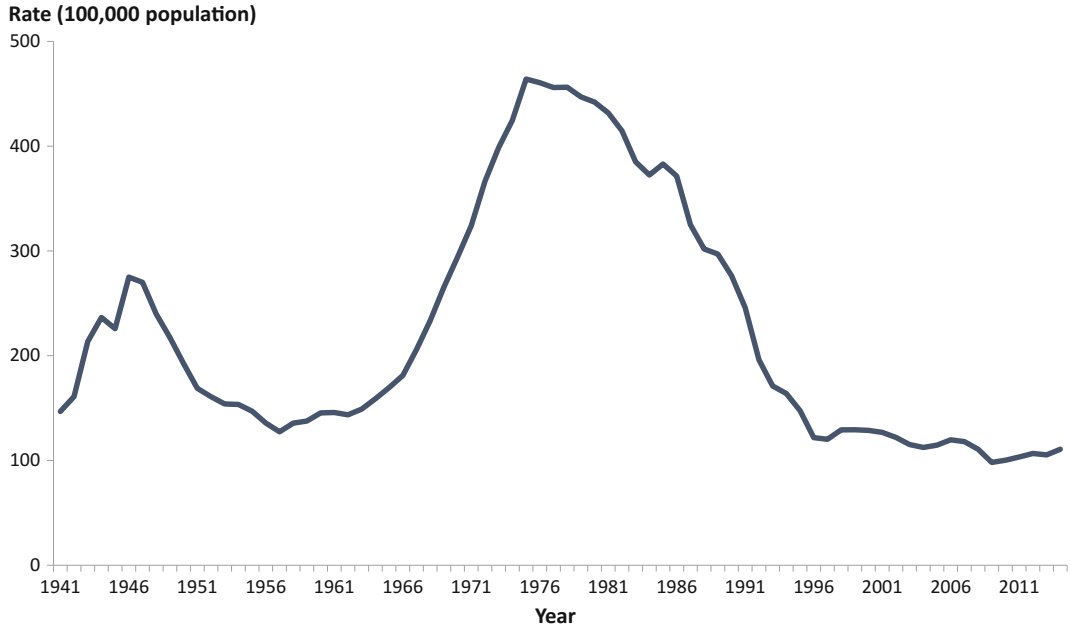

Fig. 4.1 Rates of reported gonorrhea cases by year, United States, 1941–2014. *Source* Centers for Disease Control and Prevention [18]

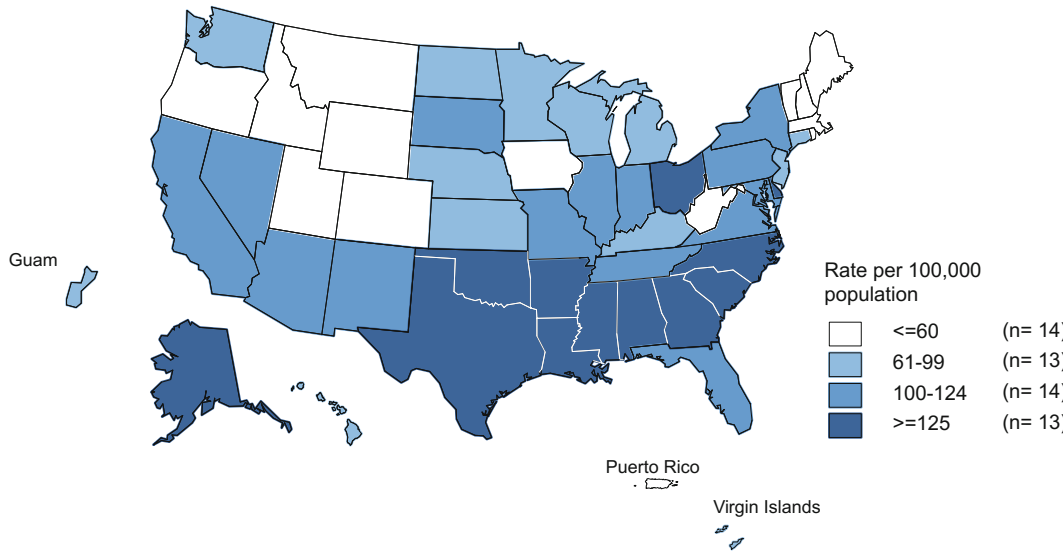

Fig. 4.2 Rates of reported gonorrhea cases by state, United States, 2014. *Source* Centers for Disease Control and Prevention [18]

sites. Supporting the possibility of increasing gonorrhea incidence in MSM, the percentage of urethral gonococcal infections attributable to MSM has steadily increased in the Gonococcal Isolate Surveillance System (GISP), a US-based sentinel surveillance system that monitors gonococcal antimicrobial susceptibility in urethral isolates [18]. Recent cross-sectional data from the multi-site sexually transmitted disease (STD) surveillance network (SSuN) demonstrate a high burden of gonorrhea among MSM attending STD clinics: among 18,568 MSM tested for gonorrhea, the median geographic site-specific gonorrhea prevalence was 19.2% (range by site: 14.5–25.3%) [18]. Additional data from SSuN collected during 2011 and 2012 demonstrated a prevalence of 11% of urogenital gonorrhea, 10.2% of rectal gonorrhea, and 7.9% of pharyngeal gonorrhea among 21,994 MSM tested for gonorrhea [20]. Notably, more than 70% of extragenital gonococcal infections were associated with negative urethral tests [20].

Over half of reported gonorrhea cases occur among African Americans, and the rate among African Americans was ten times the rate among whites in 2014 [18]. The rates among American Indians/Alaska Natives and Hispanics/Latinos were 4.2 times and 1.9 times, respectively, the rate among whites [18]. The disparities vary in magnitude by region: the disparity between African Americans and whites is highest in the Midwest and Northeast, and the disparity between American Indians/Alaska Natives and whites is highest in the Midwest and West [18]. Racial and ethnic disparities in gonorrhea incidence and prevalence are shaped in large part by differences in social determinants of health, such as socioeconomic status and differential access to health care, sexual network characteristics, sexual mixing patterns, partner concurrency, and burden of disease in geographic locations of residence and within sexual networks [21–24].

Gonorrhea is a common STI among persons with HIV. Among HIV-infected adult or adolescent MSM who underwent testing at an STD clinic participating in SSuN in 2014, 12.4% had rectal gonorrhea, 11.4% had urethral gonorrhea, and 6.7% had oropharyngeal gonorrhea (similar to prevalences found among all MSM attending SSuN-affiliated STD clinics) [18, 20]. In a prospective observational cohort of HIV-infected adults recruited from HIV specialty care clinics

in four US cities, oropharyngeal gonorrhea was detected at baseline in 3% of 365 MSM, 1% of 119 women, and 1% of 73 men who report sex exclusively with women (MSW). Rectal gonorrhea was detected in 2% of MSM and 1% of women, and genital gonorrhea was detected in 1% of MSW and women [25]. Although these percentages might seem relatively low, these percentages are several times higher than the estimated general population prevalence estimates for genital gonorrhea—0.2% in men and 0.3% in women [26].

Gonorrhea is also a substantial concern for persons at risk for, but not yet infected with HIV. Owing to heightened susceptibility to HIV in the presence of gonorrhea (as discussed above) or perhaps as an indicator of condomless sex within sexual networks that harbor STIs and HIV, the presence of gonorrhea increases the risk of subsequent HIV acquisition. Among HIV-uninfected MSM in New York City, 7% of MSM with rectal gonorrhea at baseline acquired HIV within 12 months compared to 2.5% of MSM without rectal gonorrhea at baseline [27]. In a retrospective cohort of MSM in San Francisco, men diagnosed with rectal gonorrhea or chlamydia who had two additional rectal infections in the prior 2 years were eight times more likely to seroconvert to HIV than men without prior rectal infections [28]. Among HIV-uninfected MSM in Australia, gonorrhea at any site was found to increase the risk of new HIV diagnoses within 12 months (Risk ratio 4.1, 95% confidence interval: 2.3–7.0) [29].

Clinical Presentations

The clinical presentation of gonorrhea varies by both anatomic site of infection and gender, and can range from an asymptomatic local (and sometimes self-limited) infection to serious systemic syndromes. Asymptomatic infections contribute disproportionately to *N. gonorrhoeae* transmission between partners because asymptomatic individuals are unlikely to seek medical care and abstain from sex while infected.

Genital Infections in Men

Among men, acute anterior urethritis is the most common manifestation of gonorrhea. Gonococcal urethritis is often symptomatic, presenting with dysuria and urethral discharge that ranges from scanty mucoid secretion to profuse purulent discharge (Fig. 4.3). Edema and erythema of the urethral meatus may also occur. The incubation period can range from 1 to 14 days, with most men developing symptoms within 2–5 days. If left untreated, gonococcal urethritis might spontaneously resolve after several weeks [30]. Complications of gonococcal urethritis include epididymitis (Fig. 4.4), which usually presents with unilateral testicular pain, tenderness, and swelling and a non-elevated testis (in contrast to testicular torsion), and can also include fever and prostatitis [31, 32]. Other pathogens causing epididymitis include *Chlamydia trachomatis* and, particularly among men who are the insertive partners during anal sex, enteric organisms, such as *Escherichia coli* [33]. Whereas urethral stricture due to gonococcal urethritis is widely considered a historical relic of the pre-antimicrobial era in developed countries, it may remain a complication of gonococcal urethritis in developing countries [34].

Genital Infections in Women

In women, the primary site of infection is the endocervical canal. In contrast to genital infections in men, endocervical infections in women are likely to be asymptomatic. When symptoms are present, they usually develop within 10 days of exposure. The most common symptoms include mucopurulent vaginal discharge dysuria, dyspareunia, abnormal uterine bleeding, and lower abdominal pain. Cervical examination may reveal discharge, cervical erythema and edema, and mucosal bleeding (Fig. 4.5). Purulent exudate may at times be expressed from the urethra, periurethral grands, or the Bartholin's gland duct.

The most common complication of gonorrhea in women is pelvic inflammatory disease (PID), which results from ascension of the gonococcal

Fig. 4.3 Urethral discharge from gonococcal infection. Image courtesy of Centers for Disease Control and Prevention

Fig. 4.4 Gonococcal epididymitis. Image courtesy of Centers for Disease Control and Prevention

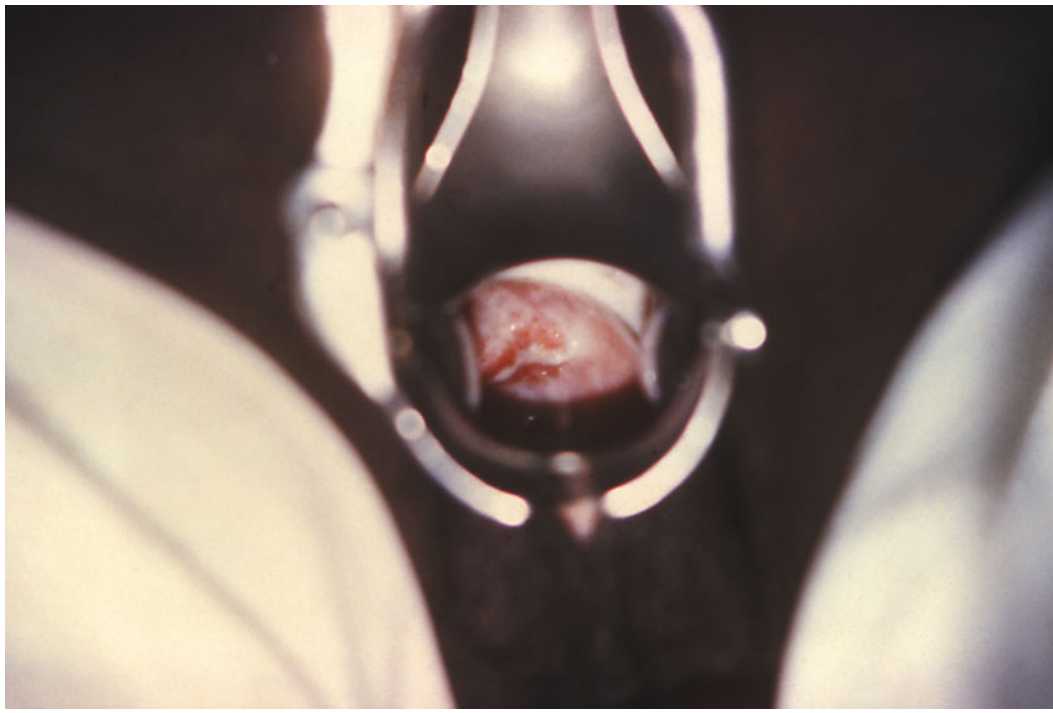

Fig. 4.5 Cervical discharge from gonococcal infection. Image courtesy of Centers for Disease Control and Prevention

infection into the uterus, fallopian tubes, ovaries, and/or pelvis. The clinical presentation of PID typically includes lower abdominal pain (classically severe and of abrupt onset during or shortly after menses), fever, cervical motion tenderness, and adnexal tenderness [35]. Evidence of lower genital tract inflammation, such as cervical discharge and friability, may also be present. PID can also present with endometritis, tubo-ovarian abscess, perihepatitis (Fitz-Hugh–Curtis syndrome), and pelvic peritonitis. Laboratory testing may demonstrate leukocytosis and increased erythrocyte sedimentation rate or C-reactive protein [35]. Recognition of PID can be challenging because symptoms may be subtle and nonspecific and diagnostic criteria are imprecise. Sequelae of PID include chronic pelvic pain, tubal infertility, and ectopic pregnancy. Infection can also result in Bartholin's gland abscess (Fig. 4.6), which presents with extreme vulvar pain and tenderness, pain with movement, walking, and sexual intercourse, erythema, fluctuance of the labia, and a palpable mass [36]. Abscesses of Skene's glands can cause pain and dysuria. In pregnant women, genital gonococcal infections are associated with chorioamnionitis, premature rupture of membranes, preterm birth, spontaneous abortions, and transmission of *N. gonorrhoeae* to the infant [37–39].

Rectal Infections

Rectal infections are due to receptive anal intercourse with an infected partner. In women, rectal infections might also occur due to perineal contamination from cervicovaginal discharge in the absence of receptive anal sex [30]. Rectal infections are most often asymptomatic. When symptoms do occur, the incubation period is typically 5–7 days and symptoms can range from mild anal pruritus and painless mucopurulent discharge to severe proctitis with pain, tenesmus, and constipation [40].

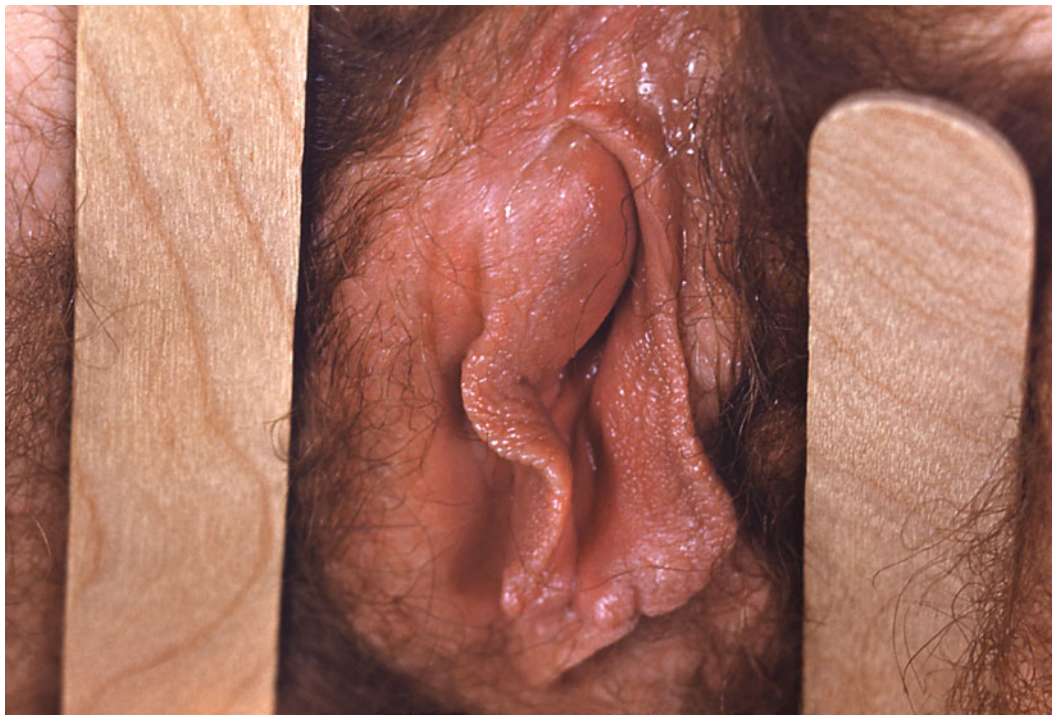

Fig. 4.6 Bartholin's gland abscess due to *Neisseria gonorrhoeae* infection. Image courtesy of Centers for Disease Control and Prevention

Pharyngeal Infections

Pharyngeal infections are acquired by oral sex exposure, including fellatio, oro-anal sex, and cunnilingus [41–43]. Similar to rectal infections, pharyngeal infections are most often asymptomatic. Infrequently, acute pharyngitis, tonsillitis, fever, or cervical lymphadenopathy can occur.

Conjunctival Infections

Although gonococcal conjunctivitis typically affects newborn infants born to mothers with genital gonorrhea (neonatal ophthalmia), it occurs infrequently in adults due to oculogenital spread, perhaps as a result of autoinoculation from an anogenital infection [44]. Gonococcal conjunctivitis can occur in the absence of urogenital infection [45]. Symptoms may be mild, but classically are hyperacute, with conjunctival hyperemia, copious purulent discharge, decreased visual acuity, eye pain with palpation, and periorbital or eyelid edema (Fig. 4.7). If not treated quickly and aggressively, conjunctival infections carry a high risk for corneal ulceration and subsequent perforation and blindness [46].

Disseminated Gonococcal Infection (DGI)

Disseminated gonococcal infection (DGI) results from bacteremia and systemic dissemination of gonococci from an untreated mucosal infection, and is thought to occur in 0.5–3% of infected patients [30]. Presentations of DGI fall roughly into one of two syndromes: (1) purulent arthritis (without skin lesions) or (2) a triad of tenosynovitis, dermatitis, and polyarthralgias. Overlap of the syndromes can occur. Purulent arthritis commonly involves the large joints of the knees (Fig. 4.8), wrists, and ankles and may present as mono- or polyarthritis. If present, polyarthritis typically is asymmetric. One series noted that

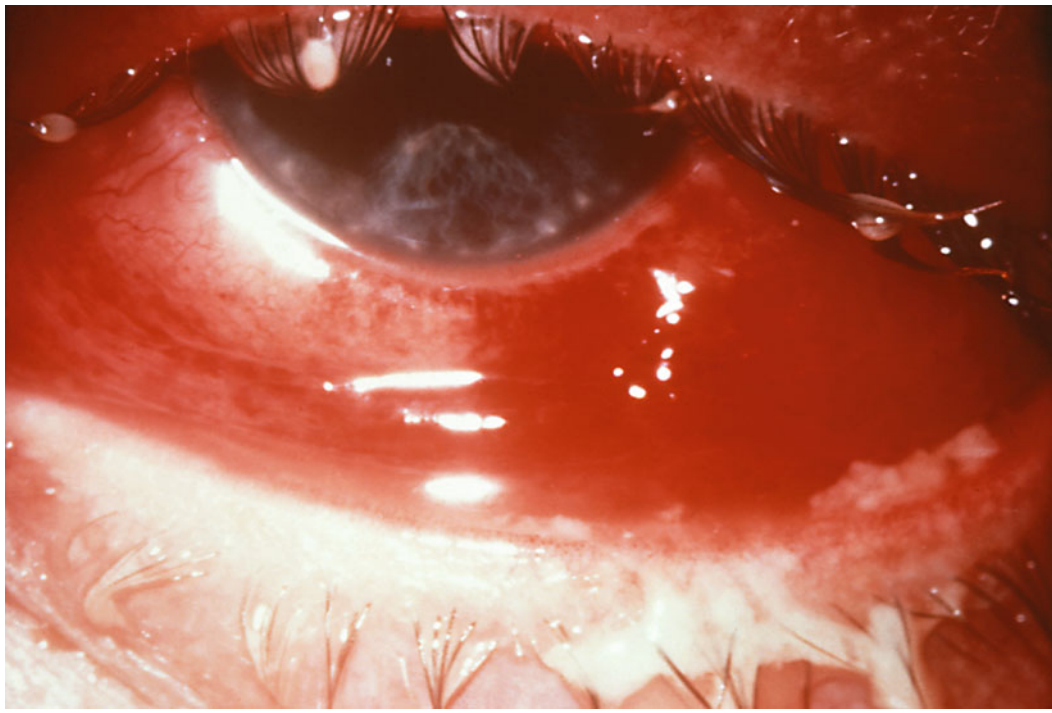

Fig. 4.7 Gonococcal conjunctivitis with purulent exudate. Image courtesy of Centers for Disease Control and Prevention

cultures of synovial fluid from joints demonstrated gonococci in fewer than one-third of probable cases, and isolation of gonococcal growth from blood cultures was even less likely [47]. The syndrome of tenosynovitis, dermatitis, and polyarthralgias often presents with fever, chills, tenosynovitis of multiple tendons (particularly the wrist, fingers, ankles, and toes), and a few painless and transient skin lesions (Fig. 4.9), often characterized as pustular or vesiculopustular [48]. Blood cultures may not demonstrate growth. Infrequently, DGI can cause endocarditis (associated with persistently positive blood cultures and valvular vegetations) and meningitis.

Diagnostic Considerations

A medical history, including a thorough sexual history with a particular focus on the gender of sex partners, anatomic sites of exposures, and sexual behavior (e.g., oral–genital intercourse; insertive versus receptive), and the physical exam are important aspects of evaluating a patient for gonorrhea. For asymptomatic patients, knowledge of the anatomic sites of exposure guides the appropriate sites for laboratory test-based screening. Even for symptomatic patients, knowledge of the sites of exposure should guide both the physical exam and decisions about whether specimens for laboratory testing should be collected from other anatomic sites. The physical exam also affords the opportunity to identify signs of other STIs.

Specific microbiological testing for *N. gonorrhoeae* should be performed in all persons at risk for or suspected to have gonorrhea [33]. Multiple laboratory test types are available for gonorrhea testing, but the recommended options are the nucleic acid amplification tests (NAAT), culture, and gram stain [49]. Other culture-independent test types which are not recommended include enzyme immunoassays, nucleic acid probe tests, genetic transformation

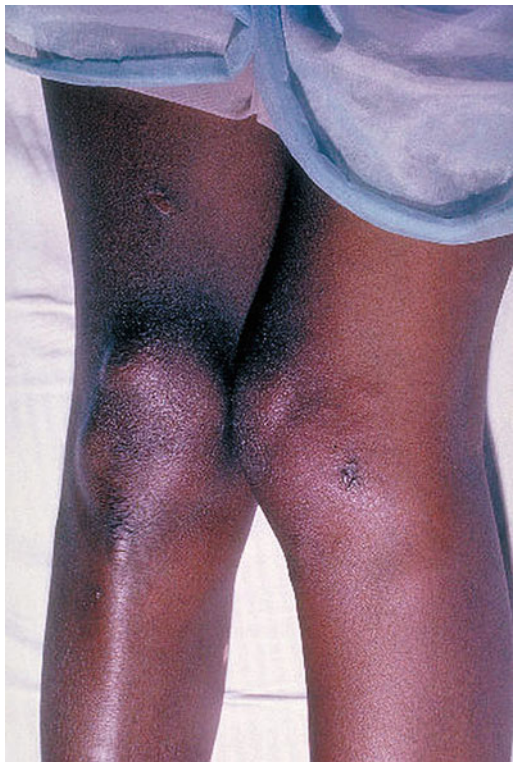

Fig. 4.8 Skin lesions and arthritic knee joints due to *Neisseria gonorrhoeae.* Image courtesy of Centers for Disease Control and Prevention

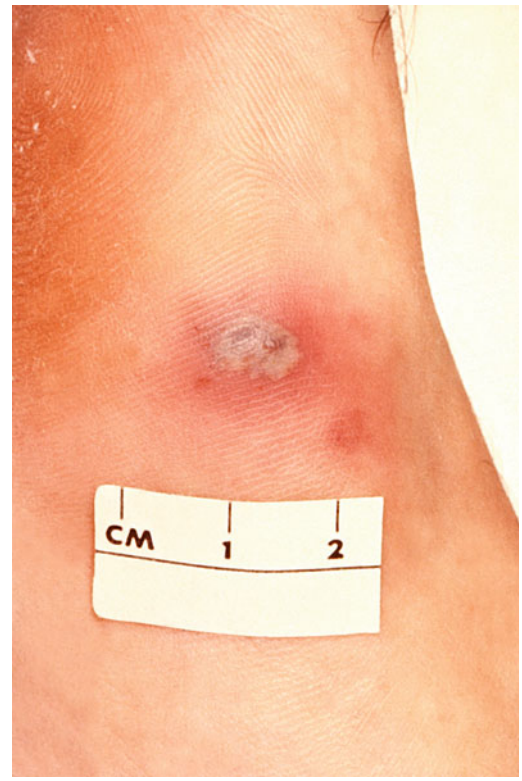

Fig. 4.9 Cutaneous lesion due to disseminated *Neisseria gonorrhoeae.* Image courtesy of Centers for Disease Control and Prevention

tests, and serologic tests that detect a systemic immune response to infection [49]. The choice of test type (or combination of test types) depends on the anatomic site of testing and rationale for testing. All persons diagnosed with gonorrhea should be tested for other STIs, including chlamydia, syphilis, and HIV.

Nucleic Acid Amplification Tests (NAATs)

The nucleic acid amplification test (NAAT) is a culture-independent laboratory test that is designed to amplify and detect nucleic acid sequences specific to the organism being detected. In comparison to other culture and culture-independent methods for gonorrhea, NAATs are far superior in overall performance, with sensitivities of well over 90% and specificities of $\geq$99%, but performance characteristics do vary by NAAT type [33, 49]. NAAT assays are recommended by CDC and have been cleared by the Food and Drug Administration (FDA) for detection of urogenital gonorrhea in men and women with and without symptoms [49]. Optimal specimen types are vaginal swabs from women, either self-collected or provider-collected, and first-catch urine specimens from men, but most commercial NAATs have been cleared by FDA to also detect *N. gonorrhoeae* in endocervical swabs, urethral swabs from men, and first-catch urine specimens from women. CDC also recommends NAATs for detection of oropharyngeal and rectal gonorrhea [49]. However, use of these nongenital specimen types has not been cleared by the FDA. Several large commercial laboratories across the United

States have established performance specifications and met Clinical Laboratory Improvement Amendments (CLIA) regulatory requirements for using rectal and pharyngeal NAATs to inform clinical management [33].

In addition to superior performance characteristics, advantages of NAATs include the ability to use less-invasive specimen types (urine and self-collected swabs) and the lack of requirement of viable organisms, thus avoiding the stringent specimen collection and handling requirements of culture for *N. gonorrhoeae*. Because of these factors, use of NAATs has facilitated expanded screening, including non-traditional healthcare settings. A disadvantage of current commercially available NAATs is that they do not allow reliable AST, which requires viable organisms.

For optimal urethral and cervical specimen collection, swabs in the test kits should be inserted 2–3 cm into the male urethra or 1–2 cm into the endocervical canal followed by two or three rotations. Rectal specimens may be collected by inserting the swab 3–4 cm into the rectal vault and rotating the swab against the rectal wall several times. Pharyngeal specimens should be collected from the posterior pharynx.

Culture

Culture in antibiotic-containing selective media (e.g., modified Thayer-Martin) is suitable for detection of *N. gonorrhoeae* from all anatomic sites. Sensitivities vary by anatomic site, probably because of differences in bacterial load by site, with the highest sensitivities for urethral specimens from men or cervical specimens from women and lower sensitivities for specimens from nongenital sites. Sensitivity and specificity also relies on proper collection and prompt transport to the laboratory.

Specimen collection processes for culture are the same as for collection for NAAT (see above). Specimens should be obtained using swabs with plastic or wire shafts and rayon, Dacron, or calcium alginate tips. Cotton swab tips might inhibit bacterial growth and should be avoided. Sampling technique can influence the yield of pharyngeal culture: inducing a gag reflex and swabbing a sufficiently large area with sufficient pressure may improve culture yield [50, 51]. The specimen should be streaked immediately onto the selective media and placed immediately into a CO_2-enriched atmosphere (e.g., a candle extinction jar or CO_2 whisk bag) for transportation to the laboratory. The specimens must then be incubated at 35–36.5 °C in an environment supplemented with 5% CO_2-enriched and examined at 24 and 48 h post-collection. Nonselective media can be used for specimens from sterile sites.

The primary advantage of isolating *N. gonorrhoeae* by culture is the ability to conduct phenotypic AST (by disk diffusion, Etest [BioMérieux, Durham, NC] or agar dilution) and genetic analysis. This is of particular importance in an era of emerging multidrug resistance and in the setting of suspected treatment failure due to antimicrobial resistance [33]. However, use of culture and access to AST has declined dramatically in the United States with the widespread adoption of NAATs. CDC encourages local and state public health laboratories in the United States to maintain culture and AST capabilities for *N. gonorrhoeae*, and clinicians and healthcare settings are encouraged to maintain necessary supplies for collection of culture specimens [49].

Microscopy and Gram Stain

The direct Gram stain of urethral discharge from men presenting with urethritis is an excellent point-of-care test for gonorrhea. Gram stain of urethral discharge that demonstrates polymorphonuclear leukocytes with intracellular Gram-negative diplococci (Fig. 4.10) has excellent sensitivity (>95%) and specificity (>99%), and can be considered diagnostic for genital gonorrhea in symptomatic men [49, 52]. Because of lower sensitivity, Gram stain of a urethral specimen should not be used to rule out gonorrhea in asymptomatic men. Gram stain of endocervical, pharyngeal, and rectal specimens is not sufficient or reliable for detection of *N. gonorrhoeae*

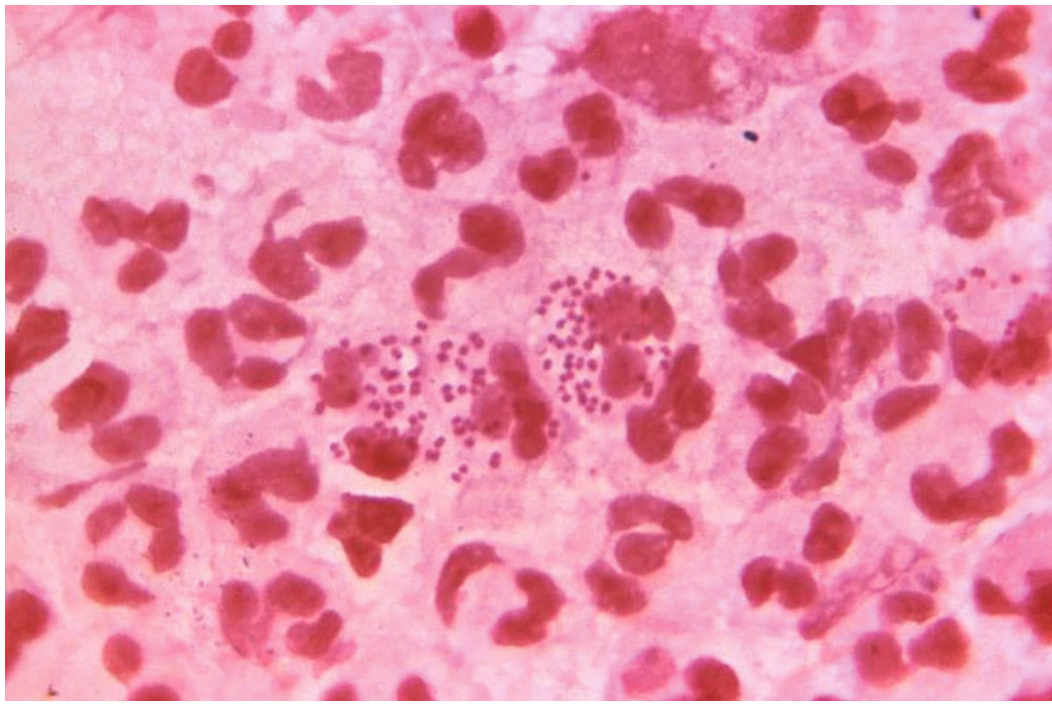

Fig. 4.10 Gram-stained smear showing polymorphonuclear leukocytes with intracellular gram-negative diplococci. Image courtesy of Centers for Disease Control and Prevention

because nonpathogenic Gram-negative diplococci can be present, and is thus not recommended [49]. Methylene blue/gentian violet stain of urethral discharge (demonstrating leukocytes with intracellular dark purple diplococci) is an alternative point-of-care test with similar performance characteristics [52].

Screening

CDC and the United States Preventive Services Task Force (USPSTF) recommend annual screening for *N. gonorrhoeae* in all sexually active women aged <25 years and for older women at increased risk of infection (e.g., multiple concurrent partners or an STI-infected partner) [33, 53]. Sexually active MSM, including those with HIV infection, should be screened for gonorrhea at all exposed anatomic sites at least annually [33]. The HIV Medicine Association recommends that all men and women with HIV be screened for gonorrhea at initial presentation and then annually if at risk for infection [54]. Because of the high reinfection rate, retesting in 3 months is recommended in men and women found to be infected [33, 54].

Despite these recommendations, gonorrhea screening rates in HIV care clinics have been suboptimal. A recent study of testing practices in HIV care clinics, using a complex-sample cross-sectional survey designed to produce nationally representative data, found that only 23% of sexually active men and women with HIV had been tested at least once for gonorrhea in the preceding 12 months [55]. Even among patients characterized as at elevated sexual risk (defined as multiple partners, illicit drug use before or during sex, or condomless sex with a casual partner, an HIV-uninfected partner, or a partner with unknown HIV status), only 26% had received a gonorrhea test in the preceding 12 months [55]. In a study of annual screening practices in 8 large HIV care clinics in 6 US

cities, only 18% of MSM were screened for urethral gonorrhea, 8.5% for rectal gonorrhea, and 7.7% for pharyngeal gonorrhea [56].

Barriers to gonorrhea screening of persons with HIV include perceived time constraints when caring for medically complex HIV-infected patients, discomfort taking sexual histories and conducting genital examinations, lack of provider awareness that NAAT can be performed on extragenital specimens, lack of provider awareness of CDC STD screening guidelines, cultural and language barriers, and perceptions that patients were reluctant to be screened [57, 58]. Education of clinic staff and implementation of a clinic-based risk assessment tool for male patients has been associated with improved gonorrhea screening rates, particularly for pharyngeal infections [59]. Other interventions that may increase screening include strategic placement of specimen collection materials or automatic urine collection, electronic health record (EHR) reminders, and patient testing reminders [60].

Treatment

Gonorrhea is most often treated empirically and clinicians base the choice of antimicrobial regimen on established treatment guidelines, such as the CDC STD Treatment Guidelines [33]. Treatment guidelines are heavily informed by prevalence of antimicrobial resistance from surveillance data, and revisions to treatment guidelines are often driven by results of surveillance data demonstrating the emergence of resistance to a recommended agent. Traditionally, CDC has only recommended antimicrobial regimens with efficacy of $\geq 95\%$ (and thus prevalence of resistance of <5%), so as to reliably cure the infection, prevent sequelae, and prevent transmission to sex partners [61].

Prior to the introduction of antimicrobial agents, gonorrhea was often treated with purgatives, diuretics and laxatives, bleeding and leeching, perineal blistering, oral administration of turpentine seasoned with lemon juice, urethral irrigation with mercury, iodide and silver nitrate, forcible retention of urine with forceps, and the insertion of bougies or sounds (solid rods) into the urethra to remove strictures [1, 62]. Fortunately, the introduction of sulfonamides (1936) and penicillin (1943) provided safe and effective antimicrobial therapy and revolutionized gonorrhea treatment. Not only were infections cured and sequelae prevented, but effective therapy curtailed transmission to partners. Detection of infection followed by prompt and effective antimicrobial therapy has largely become the cornerstone of public health gonorrhea control efforts in the United States.

Administration of effective gonorrhea treatment has been complicated by repeated gonococcal acquisition of antimicrobial resistance. Resistance to sulfonamides emerged within several years of the introduction of these agents [63]. For several decades during the twentieth century, the stepwise accumulation of chromosomal mutations conferring increasing penicillin resistance was able to be overcome with increasing the dosage of penicillin and prolongation of sufficient serum penicillin concentrations with probenecid [64]. In the late 1970s, however, penicillinase-producing *N. gonorrhoeae* (PPNG) emerged and rendered penicillin ineffective [65]. Resistance to tetracyclines developed in the 1980s, undermining the effectiveness of minocycline and doxycycline [66]. Fluoroquinolone-resistant strains (QRNG) later emerged in East Asia and as demonstrated by surveillance data from CDC's Gonococcal Isolate Surveillance Project (GISP), spread to the United States by the 2000s, emerging initially in Hawaii, before spreading to the West Coast, among MSM, and then eastward across the continental United States [67–69]. By 2007, CDC no longer recommended fluoroquinolones for gonorrhea treatment [69]. Third-generation cephalosporins (i.e., oral cefixime and injectable ceftriaxone) were the only antimicrobials recommended. However, the effectiveness of these drugs has been threatened by the global spread of strains with reduced cefixime susceptibility. Cases of ceftriaxone-resistant infections have been identified in Japan, France, and Spain [70–72]. Data from GISP also demonstrated declining

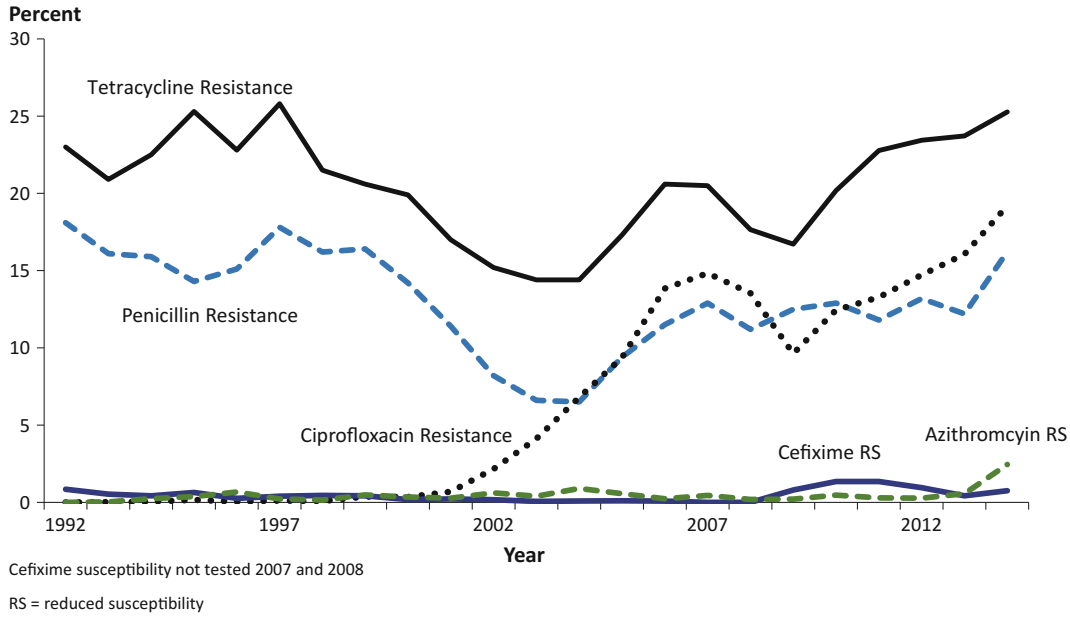

Fig. 4.11 Prevalence of penicillin, tetracycline, and ciprofloxacin resistance and reduced susceptibility to cefixime or azithromycin in urethral *Neisseria gonorrhoeae* isolates, Gonococcal Isolate Surveillance Project, United States, 1987–2014. *Source* Gonococcal Isolate Surveillance Project (GISP), Centers for Disease Control and Prevention

cefixime susceptibility among gonococcal strains in the United States, particularly in the Western United States and among MSM [73]. Many of these isolates with reduced cefixime susceptibility are resistant to other previously recommended antimicrobials, such as penicillin, tetracycline, and ciprofloxacin. In response to declining cefixime susceptibility, CDC changed gonorrhea treatment recommendations in 2010, 2012, and 2015 [33, 74, 75]. Among all isolates in GISP, resistance to previously recommended antimicrobials remains common (Fig. 4.11).

Uncomplicated Cervical, Urethral, and Rectal Gonorrhea

Currently, CDC recommends dual therapy of ceftriaxone 250 mg as a single intramuscular dose plus azithromycin 1 g orally for treatment of infections of the urethra, cervix, pharynx, and rectum (Table 4.1) [33]. Azithromycin should be administered regardless of whether chlamydial infection is present or absent. To maximize adherence, medication for gonorrhea should ideally be provided on site and directly observed. The treatment recommendations do not differ for persons with HIV.

The rationale for recommending dual therapy rests on the theoretical basis of using two antimicrobial agents with different molecular mechanisms of action to improve treatment efficacy (especially if treating an infection resistant to one of the agents) and potentially slowing the emergence and spread of resistance to cephalosporins [33]. The lack of alternative first-line agents adds urgency to the need to prolong the effectiveness of cephalosporins for as long as possible. Azithromycin is preferred as the second agent because it is single dose and the prevalence of reduced azithromycin susceptibility remains low in the United States, especially among isolates with reduced cephalosporin susceptibility. In contrast, doxycycline is not favored as the second agent because the prevalence of resistance to tetracycline remains high (Fig. 4.11).

Table 4.1 Preferred treatment of *N. gonorrhoeae* by condition

Uncomplicated infections of the cervix, urethra, and rectum Ceftriaxone 250 mg IM in a single dose PLUS Azithromycin 1 g orally in a single dose
Uncomplicated infection of the pharynx Ceftriaxone 250 mg IM in a single dose PLUS Azithromycin 1 g orally in a single dose
Gonococcal conjunctivitis Ceftriaxone 1 g IM in a single dose PLUS Azithromycin 1 g orally in a single dose
Disseminated gonococcal infection: arthritis and arthritis–dermatitis syndrome Ceftriaxone 1 g IM/IV every 24 h PLUS Azithromycin 1 g orally in a single dose
Disseminated gonococcal infection: endocarditis or meningitis Ceftriaxone 1–2 g IV every 12–24 h PLUS Azithromycin 1 g orally in a single dose

Created with data from [33]

Many other countries recommend similar dual therapy regimens, but providers practicing outside of the United States are encouraged to be aware of local susceptibility data and consult relevant national treatment guidelines.

If ceftriaxone is not available, the dual therapy regimen of cefixime 400 mg orally in a single dose and azithromycin 1 g orally in a single dose can be considered for uncomplicated cervical, urethral, and rectal infections. Allergy to cephalosporins is uncommon, even in patients with a history of penicillin allergy [76–78]. However, patients with a history of a severe IgE-mediated penicillin allergy (such as anaphylaxis, Steven Johnson syndrome, and toxic epidermal necrolysis) should not receive cefixime or ceftriaxone. Treatment options for such patients include the combination of gentamicin 240 mg as a single intramuscular dose (often divided into 2 injections of 120 mg) plus azithromycin 2 g orally, or the combination of gemifloxacin 320 mg orally plus azithromycin 2 g orally [77]. Shortages of gemifloxacin have been reported in the United States.

To minimize disease transmission, persons treated for gonorrhea should be instructed to abstain from sexual activity for 7 days after treatment and until all sex partners are adequately treated. Patients should also be educated on correct and consistent condom use to prevent reinfection.

Uncomplicated Pharyngeal Gonorrhea

Gonococcal infections of the pharynx are more difficult to eradicate than genital and rectal infections, probably because of differential drug penetration. Pharyngeal gonorrhea should be treated with dual therapy of ceftriaxone 250 mg as a single intramuscular dose plus azithromycin 1 g orally. If pharyngeal gonorrhea is treated with an alternative regimen, the patient should be asked to return 14 days after treatment for a test-of-cure, either by NAAT or culture [33]. If the NAAT is positive, a confirmatory culture should be performed before retreatment; positive test-of-cure cultures should undergo AST.

Conjunctivitis

Treatment data on gonococcal conjunctivitis are limited. Currently, CDC recommends dual therapy with ceftriaxone 1 g intramuscularly as a single dose and azithromycin 1 g orally in a single dose [33].

Disseminated Gonococcal Infection (DGI)

Initial management of DGI should include hospitalization and clinical evaluation for endocarditis and meningitis. For purulent arthritis or arthritis–dermatitis syndrome, CDC recommends ceftriaxone 1 g intramuscularly or intravenously every 24 h plus azithromycin 1 g orally in a single dose [33]. Oral therapy can be considered 24–48 h after substantial clinical improvement and should be guided by results of AST. Patients should be treated for at least 7 days.

For gonococcal meningitis or endocarditis, patients should be treated with ceftriaxone 1–2 g intravenously every 12–24 h plus azithromycin 1 g orally in a single dose [33]. Therapy should be guided by results of AST and by consultation with an infectious disease specialist. Optimal duration of therapy is unclear, but CDC recommends that parenteral therapy be continued for 10–14 days for meningitis and at least 4 weeks for endocarditis.

Partner Management

Recent sex partners (from within 60 days prior to symptom onset) should be referred for evaluation, testing, and presumptive dual therapy [33]. For heterosexual patients whose partners are unable or unwilling to promptly access care, providers can consider expedited partner therapy, in which a prescription or medications are given to the patient to deliver to the partner(s). Written educational materials, which outline the reason for the medication, the importance of treatment, and when to seek clinical evaluation, should accompany the prescription or medications. Materials for women should include educational material about PID. No data exist on efficacy of expedited partner therapy in MSM. Providers can refer to the frequently updated CDC EPT website for the legal status of EPT in their state (http://www.cdc.gov/std/ept/legal/default.htm).

Suspected Treatment Failures and Antimicrobial Resistant Infections

In light of evidence pointing to emerging resistance to cephalosporins, clinicians should be vigilant for possible treatment failures due to antimicrobial resistance. In the United States, most suspected treatment failures are likely to be due to reinfections, rather than antimicrobial resistance. In patients in whom reinfection is unlikely (e.g., denial of sexual activity since treatment) and treatment failure is suspected, relevant specimens should be collected for culture and simultaneous NAAT prior to retreatment [33]. If *N. gonorrhoeae* is detected by culture, the isolate should undergo phenotypic AST to evaluate for resistance. Patients should be strongly encouraged to ask their recent partners to present to medical care for evaluation and treatment. In the United States, the provider should notify the local or state health department STD program within 24 h, and the health department is encouraged to notify CDC.

Because many suspected treatment failures are due to reinfections, patients can be retreated with dual therapy ceftriaxone 250 mg intramuscularly and azithromycin 1 g orally if reinfection is considered likely. Additional options, especially for patients in whom a resistant infection is strongly suspected, include dual therapy with gentamicin 240 mg intramuscularly and azithromycin 2 g orally or dual therapy with gemifloxacin 320 mg orally and azithromycin 2 g orally [79].

Conclusions

Despite its ancient origins and the availability of effective antimicrobial therapy, gonorrhea remains common, especially in populations at risk for HIV. Although rates of gonorrhea in the United States are at historic lows, recent increases in rates among men and emerging multidrug resistant strains in the United States and worldwide are of concern. The interaction between HIV and gonorrhea may contribute to enhanced HIV transmission and acquisition and might have deleterious virological and immunological consequences for persons with HIV. In addition, incident gonorrhea in HIV-infected persons is a marker of recent condomless sex, potentially placing the patient at risk for other STDs and his or her partners at risk for STDs and HIV acquisition. Gonorrhea can be prevented with correct and consistent condom use, avoidance of sexual activity, or monogamous sexual activity with an uninfected partner. Regular screening of patients at risk for gonorrhea, appropriate laboratory testing of specimens from exposed anatomic sites, and treatment with CDC-recommended dual therapy prevents complications from gonorrhea and continued transmission.

Disclaimer The findings and conclusions in this chapter are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Syphilis

5

James Lewis and Arlene C. Seña

Introduction

Syphilis is a sexually transmitted infection (STI) caused by the spirochete *Treponema pallidum* subsp. *pallidum*. Included in the genus of *Treponema* are three other known human pathogens: *T. pallidum* subsp. *endemicum*, the causative agent of endemic syphilis or bejel; *T. pallidum* subsp. *pertenue*, the causative agent of yaws; *Treponema carateum*, the causative agent of pinta. This chapter will focus on subsp. *pallidum* [1]. In addition to sexual and vertical transmission, syphilis can be transmitted via blood transfusion and organ transplantation [2–4].

Syphilis is one of the oldest described bacterial diseases. The first well-described outbreak of syphilis dates back to 1494 in Naples, Italy, contributing to the theory that syphilis was imported by Christopher Columbus and his crew from the Americas. "The Great Pox" rapidly spread through Europe and into Asia during the fifteenth and sixteenth centuries [5, 6]. However, the etiologic agent *T. pallidum* was not discovered until 1905 by Schaudinn and Hoffmann. Shortly thereafter, Wassermann invented the first serologic test for syphilis in 1906, which provided the basis for modern non-treponemal tests [1, 5, 7]. Early therapy for syphilis included mercury and arsenic compounds, but the discovery of penicillin by Fleming in 1943 provided the most effective treatment. The incidence of syphilis peaked in the 1940s at 66.9 cases per 100,000 population, but rapidly decreased with the introduction of penicillin to 3.9 cases per 100,000 population in 1956 [1, 5, 8, 9].

Since 1956 syphilis incidence has waxed and waned on an approximately 10-year cycle. It is unclear why this has occurred, and some experts have suggested that it is based on syphilis antigenic variation and loss of herd immunity. That each of the outbreaks has occurred among separate sociocultural groups argues against this phenomenon [5, 8, 9]. For example, syphilis in the 1970s and early 1980s disproportionately affected the men who have sex with men (MSM) population, while it became more prominent in the heterosexual African-American population in the late 1980s and early 1990s in association with crack cocaine and trade of sex for drugs and money [5, 8]. Given these data, it is more likely that the cycling is due partly to low-level endemicity, with periodic increases in socially marginalized groups with high rates of partner exchange, poor access to health care, and other societal factors [9]. Due to penicillin and concerted public health efforts, the rate of syphilis declined to an all-time low in the late 1990s [5, 10]. Unfortunately, the incidence of syphilis has steadily increased in the twenty-first century, primarily affecting developed countries

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including the United States (US), China, Western Europe, and Australia. The current epidemic mainly involves MSM and disproportionately affects young ethnic minorities and HIV-infected populations [9, 11–13]; recent estimates are also showing increases among heterosexual communities [1, 5]. Within the MSM community, coinfection with HIV has been found to be an independent risk factor for syphilis infection. Syphilis acts synergistically with HIV leading to a two- to fivefold increased risk of HIV acquisition and transmission in persons with symptomatic syphilis. Modeling studies have therefore indicated that effective syphilis control would have a significant impact on HIV prevention efforts [14].

Basic Science

Basic science research with syphilis has been greatly hampered by the inability to continuously cultivate *T. pallidum* in vitro, mostly due to extreme lability associated with its cytoplasmic outer membrane layer. Animal models have been developed with some success; however, while many animals can be successfully infected, only a few will manifest symptoms. The rabbit model is the best syphilis animal model described as it has a natural venereal disease cycle with the spirochete *Treponema paraluiscuniculi.* Rabbits will demonstrate primary and secondary lesions of syphilis infections as well as asymptomatic chronic infection which persists throughout the remainder of life [14].

Immune Response to Syphilis and Relevance to HIV Coinfection

Human and rabbit studies have shown that *T. pallidum* is cleared from lesions via a Th1 predominant response utilizing IFN-γ and opsono-phagocytic killing [14]. While syphilis infection has not been shown to increase HIV viral load (VL) in semen, it has been shown to cause an increase in serum VL and a drop in CD4 count [15]; in addition it has been shown to cause increased HIV transmission risk by a variety of mechanisms [16]. During the immune response to syphilis infection, the expression of CCR5 (an HIV co-receptor) is induced in phagocytic macrophages. Because macrophage tropic HIV has been shown to be the most infective form of HIV, this response to syphilis infection can potentiate HIV transmission [17–20]. Additionally, the immune response to syphilis has been shown to involve mobilization of NF-κB [20]. This cellular transcription factor has been implicated in the regulation of HIV-1 gene expression [20]. The increase in NF-κB expression during syphilis infection has been correlated with increased HIV-1 gene expression especially in macrophages, which could also potentiate HIV transmission in coinfected individuals [15, 19, 20].

Case Illustration

A 26-year-old previously healthy male presents with symptoms of Bell's Palsy associated with mild scalp pain posterior to the left ear, and left-sided hyperacousia. He was initially evaluated in the emergency department, and provided treatment with acyclovir for presumptive shingles. Within 2 weeks of his initial presentation, he developed a centripetal maculopapular rash involving his palms and soles in conjunction with fever, malaise, and headache. He denied any ocular or other meningeal symptoms. He was prescribed doxycycline for presumed Rocky Mountain Spotted Fever and referred for immediate infectious disease consultation. The patient reported that he had performed unprotected oral sex on two male partners in the last 6 months. RPR titer on the day of evaluation was 1:512 with a reactive confirmatory treponemal assay and his fourth-generation HIV test was positive. Because of his symptoms, the patient underwent a lumbar puncture and cerebrospinal fluid (CSF) analysis revealed 30 nucleated cells,

protein of 33 mg/dL, glucose of 48 mg/dL, and a nonreactive CSF VDRL. Considering his presentation and abnormal CSF findings despite a negative CSF VDRL, the patient was treated for neurosyphilis with penicillin G via IV infusion for 14 days.

This case is interesting because it brings forth key points regarding HIV and syphilis care involving neurosyphilis and its evaluation. This case illustrates the common occurrence of HIV and syphilis coinfection [18] and the propensity of HIV coinfected individuals to develop early symptomatic neurosyphilis [21]. The presentation provides an example of syphilis' ability to mimic other illnesses as "the great imitator," and the importance of considering syphilis in the differential even when the presentation is not classic.

Epidemiology

Worldwide, syphilis remains a leading cause of genital ulcer disease, second only to herpes. Despite large increases in incidence in developing countries, the majority of cases are still located in sub-Saharan Africa and Southeast Asia [5, 22]. The most recent data from the World Health Organization (WHO) in 2008 reported a stable yearly incidence of 10.6 million cases and 36.4 million prevalent cases of syphilis [23].

In the US, the incidence of syphilis reached an all-time low in 2000, but has risen steadily since 2001 [11]. The proportion of syphilis cases attributable to MSM rose from 7% in 2000 to 64% in 2004; in 2013, MSM accounted for 75% of new cases [9, 24]. Experts have theorized that the MSM syphilis epidemic is in part due to the success of anti-retroviral therapy (ART) leading to increased high-risk sexual behaviors among HIV-infected MSM; it also likely has to do with the increased practices of HIV serosorting and finding sexual partners through the Internet, circuit parties, and bath houses [5, 8, 25].

HIV-infected MSM are disproportionately affected by the current syphilis epidemic, with 20–70% of MSM with syphilis being coinfected with HIV [26, 27]. Additionally, it has been found that syphilis has a prevalence of ~10% within the HIV-infected community, and syphilis, as well as other STI prevalence has been found to be the highest at the time of HIV diagnosis [28]. Because syphilis can affect the transmission of HIV, there is concern about the risk of increasing HIV incidence in the setting of the current syphilis epidemic. A recent study conducted in New York found that 1 in 20 MSM diagnosed with syphilis were diagnosed with HIV within 1 year [29]. It is not entirely understood why HIV incidence seems to have been unaffected by the syphilis epidemic in the US to date; one of the reasons behind this observation may be increased serosorting, in which HIV-infected individuals are more likely to have sexual interactions with other HIV-infected persons as a risk-reducing strategy [30]. However, serosorting could lead to a higher reinfection rate of syphilis after its introduction to a closed sexual network of HIV-infected partners [31].

Clinical Presentation

Because *T. pallidum* disseminates quickly to all tissues of the body after infection, the manifestations of disease are quite variable and can involve any organ system [6]. Clinical presentations can be acute or chronic and are divided into early and late stages based on symptoms and time since initial infection [1, 6, 32]. The early stage can be divided into primary, secondary, and early latent phases, and the late stage into late latent and tertiary phases (Table 5.1) [1, 6]. Congenital syphilis, not discussed in this chapter, is also divided into early and late stages [6]. HIV-infected patients have been shown, generally, to have a similar natural history of syphilis infection (Fig. 5.1) as compared to HIV-uninfected patients with a few notable and rare exceptions, mostly relating to early stages of disease which will be discussed below [6].

Table 5.1 Clinical manifestations of syphilis

Stage of syphilis	Typical manifestations	Time to onset (range)	Manifestations prevalent in HIV-infected patients
Early stage			
Primary	Chancre, regional lymphadenopathy	3 weeks (3–90 days)	Multiple chancres, deeper chancres
Secondary	Rash, fever, malaise, generalized lymphadenopathy, mucus patches, condyloma lata, renal disease, gastric disease, alopecia	2–12 weeks (2 weeks–6 months)	Ulceronodular syphilis (still rare)
Hepatitis	Elevated liver enzymes (ALP > AST/ALT), normal bilirubin	2–12 weeks (2 weeks–6 months)	More common in HIV up to 30% prevalence
Neurosyphilis			
Asymptomatic	None	Unknown, likely within days	Reportedly more common in HIV, unclear clinical significance
Acute meningitis	Headache, meningismus, confusion	<2 years	More common in HIV-infected patients
Ocular	Uveitis, keratitis, optical neuritis	<2 years	Likely more common in HIV-infected patients with increasing prevalence
Early latent	None	<1 year	
Late stage			
Late latent	None	>1 year	
Neurosyphilis			
Meningovascular	Stroke-like symptoms, cranial nerve palsies	5–12 years	Rare
Paresis	Early: headache, vertigo, personality changes	15–20 years	Rare
	Late: psychosis, mania, delusion, acute vascular events		
Tabetic	Dementia, lightning pains, loss of vibration sense and proprioception, ataxia, ocular palsies, Argyll Robertson Pupil	20–25 years	Rare
Tertiary			
Cardiovascular	Aortic aneurysm, aortic insufficiency, coronary ostial stenosis	10–30 years	Cases reported but still very rare
Gumma	Tissue destructive immune mediated lesions occurring in any organ, usually skin or bone	15 years (1–46 years)	Rare

Primary Syphilis

The primary phase of syphilis is limited to chancre formation approximately 3 weeks after inoculation (10–90 days) (Fig. 5.2). Chancres are usually present on the genitals but can appear anywhere at the site of inoculation including the rectum/anal canal and oral cavity. The chancre is usually solitary but there can be multiple genital ulcers. Lesions are usually indurated, painless, non-purulent, have a clean base, and can be associated with regional lymphadenopathy. Chancres typically last for days to weeks and can resolve spontaneously without treatment, as the infection progresses to disseminated infection. HIV-infected patients have a similar natural history of primary disease, but they have a higher frequency of multiple chancres (up to 70% of

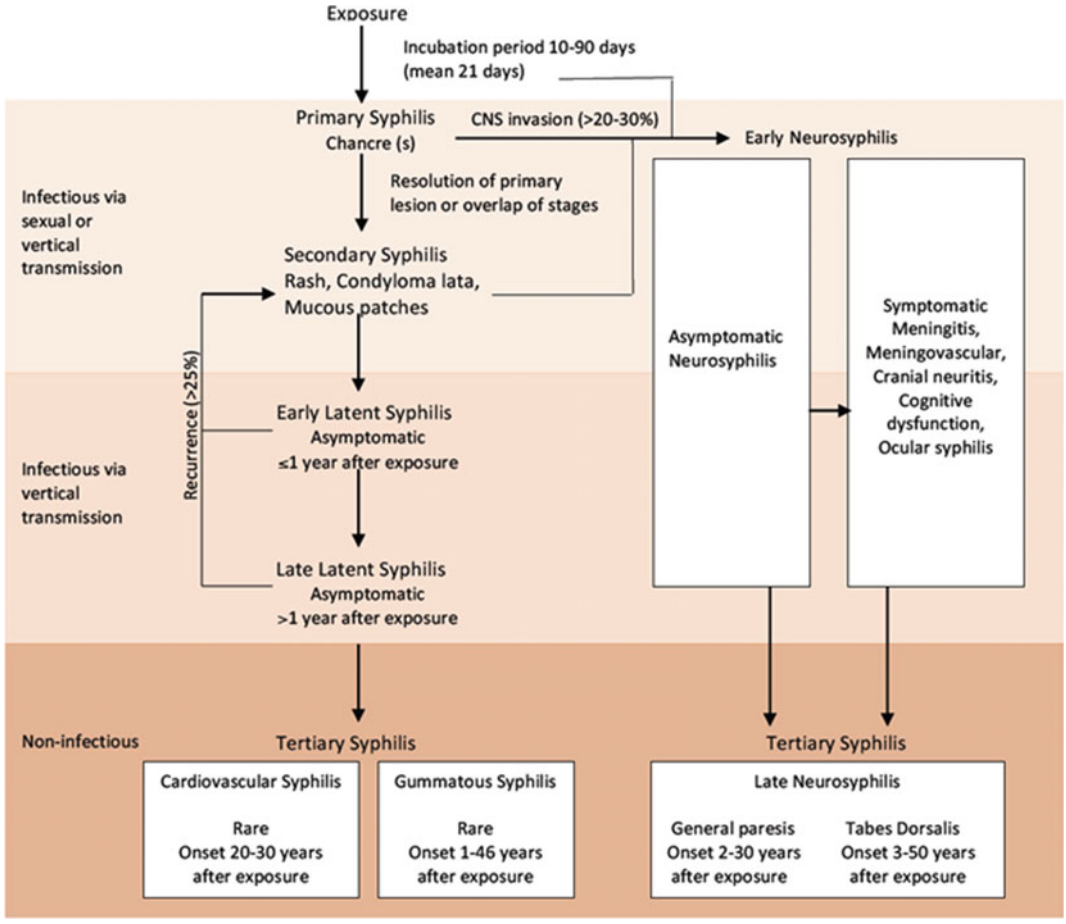

Fig. 5.1 Natural history of untreated syphilis in HIV coinfected patients. Adapted with permission from Ho and Lukehart [17]

cases), larger or deeper lesions, and up to a quarter of HIV-infected patients can have concomitant primary and secondary signs [6, 26].

Secondary Syphilis

The secondary or disseminated stage of syphilis generally occurs within 3 months of infection and can present with a wide variety of signs and symptoms due to multiple organ involvement. The classic and most common sign of secondary syphilis is a mucocutaneous rash with pale "copper-colored" discrete maculopapular lesions that begin on the trunk and proximal extremities and spread to distal extremities including the palms and soles (Fig. 5.3) [1, 6]. Symptoms during this phase can include generalized lymphadenopathy, sore throat, myalgia, and constitutional symptoms which can range from malaise to prostration and cachexia [1, 6]. When the rash involves the hair follicles, it can cause alopecia with a "moth-eaten" appearance. There are numerous less common manifestations of early or secondary syphilis as well discussed below grouped by organ system.

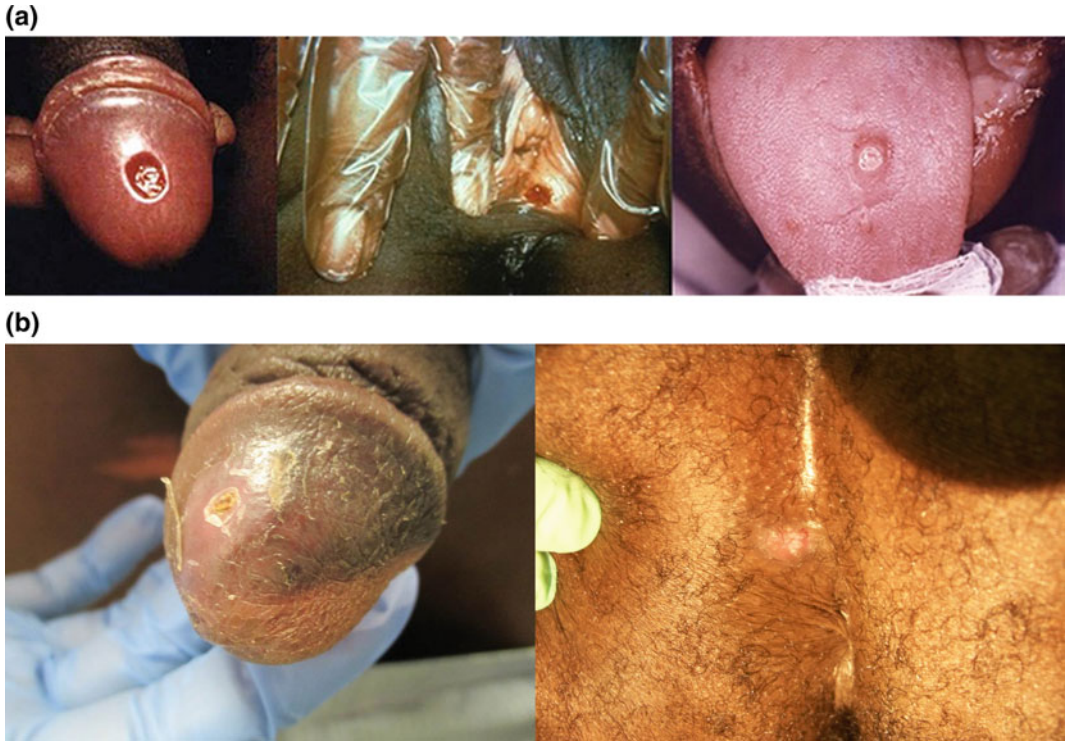

Fig. 5.2 **a** Primary syphilis chancres. Images obtained from http://www.cdc.gov/std/syphilis/images.htm. **b** Examples of resolving primary syphilis chancres

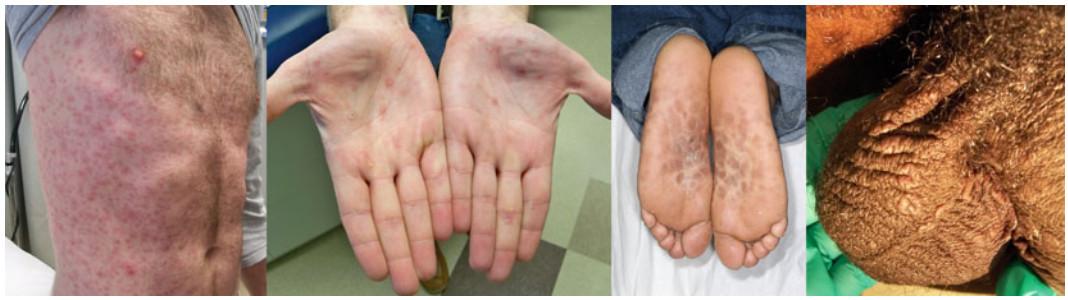

Fig. 5.3 Secondary syphilis rash

Other Skin/Mucus Membrane Manifestations

Mucus patches (Fig. 5.4a) consist of localized inflammation of the tongue, oral cavity, and genital mucus membranes. Condyloma lata (Fig. 5.4b,c) are usually concurrent with the typical secondary syphilis rash and are enlarged lesions in warm moist areas such as the perineum and anus. Both mucus patches and condyloma lata are highly infectious with a large treponemal burden. Lues maligna, also known as ulceronodular and malignant syphilis, is a severe form of secondary syphilis characterized by pustular necrosis of secondary syphilis lesions and more severe symptoms including fever, headache, and

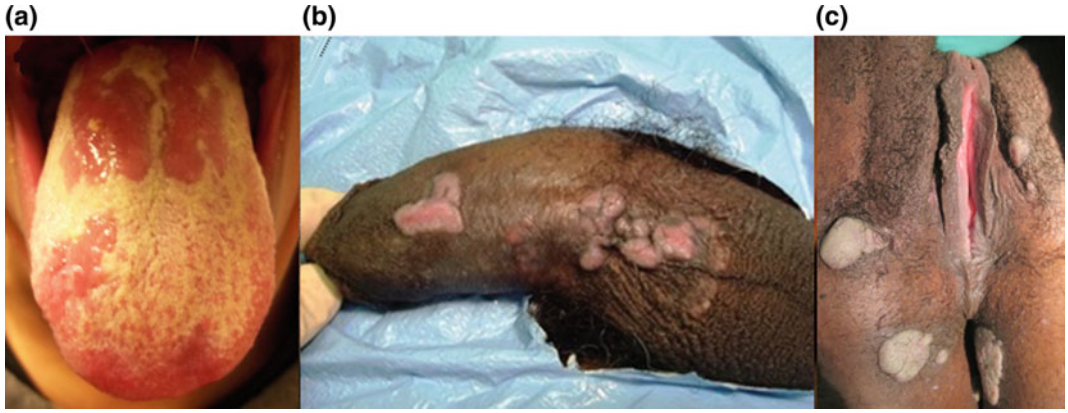

Fig. 5.4 **a** Mucus patch on tongue. **b** Condyloma lata on penis. Image obtained from http://www.cdc.gov/std/training/picturecards.htm. **c** Condyloma lata in female

myalgia [1, 6]. This syndrome has been reported to be more common, although still rare, in HIV-infected patients [33].

Gastrointestinal Syphilis

Hepatitis is a rare but increasingly frequent manifestation of secondary syphilis, especially in HIV-infected patients. Elevation of liver function tests due to syphilis are characterized by a disproportionate rise in alkaline phosphatase relative to the transaminases and gamma-glutamyl transpeptidase, with normal bilirubin [34]. It is unclear if syphilitic hepatitis is immune mediated or a result of direct treponemal invasion [34]. Recent studies in the US have revealed a prevalence of 1–38% prevalence in HIV-infected patients; because of this increasingly prevalent condition, syphilis should be on the differential for HIV-infected patients presenting with hepatitis [34]. Gastric syphilis can also occur, and is characterized by mucosal erosions, rugal hypertrophy, or shallow ulcers in the antral or pyloric regions [1].

Early Neurosyphilis

Neurosyphilis (NS) can occur during early and late stages; the majority of cases are likely occurring in HIV-infected patients due to the high rates of coinfections and the higher likelihood of early NS in this population, but the epidemiology is not well defined due to lack of population level data [35]. Asymptomatic neurosyphilis (ANS) can occur in early syphilis and latent phases with a prevalence of 13–20% and a peak incidence at 12–18 months after infection. In the pre-antibiotic era, this would predict increased risk for development of late stage NS, but in the modern era, the diagnosis of ANS is of unclear utility [35].

Symptomatic NS can present as acute syphilitic meningitis in early or late stages of syphilis, with meningismus, nausea, vomiting, cranial nerve palsies, and rarely seizures, sometimes mimicking HSV encephalitis [35]. Meningovascular, and the forms of parenchymatous NS will be discussed in the "Late Stage" section of this chapter.

Ocular Syphilis

There has been a recent concern for increased incidence of ocular syphilis, which is a clinical manifestation of NS, in both HIV-infected and HIV-uninfected persons in association with early syphilis. The classical presentation is anterior uveitis, although posterior and panuveitis may be more common in HIV-infected patients. The uveitis can include findings of white pre-retinal

opacities and placoid uveitis on ophthalmologic evaluation. Recent reports suggest a higher risk of ocular syphilis in HIV patients with lower CD4 counts [36, 37]. Other manifestations of ocular syphilis include episcleritis, keratitis, hypopyon, iridocyclitis, vitreitis, chorioretinitis, retinal vasculitis, inflammatory disc edema, and neuroretinitis [36]. All individuals suspected of having ocular syphilis should undergo a CSF examination.

Renal Syphilis

Renal syphilis usually presents as proteinuria but can range from nephrotic syndrome to acute nephritic syndrome, rapidly progressive glomerulonephritis and renal failure. This disease is usually immunogenic resulting from damage inflicted by immunoglobulin-treponemal antigen complexes within the glomeruli [1, 6].

Early Latent Syphilis

The lesions of secondary syphilis usually resolve within 3 months, after which symptoms are absent for an extremely variable period of time. This asymptomatic period is referred to as the latent phase and this is split into early latent (within one year after initial infection) and late latent stages (greater than one year after initial infection). Up to 25% of patients can have recurrent secondary lesions during the early latent phase. During the latent phases sexual transmission is unlikely, but vertical transmission is possible due to intermittent spirochetemia [6].

Late Latent Syphilis

The late latent phase of syphilis is clinically identical to early latent, but during this phase there is a lower likelihood of relapse to secondary syphilis manifestations. The late latent stage ends with treatment or development of tertiary disease. Vertical transmission is possible during this phase [1, 6].

Late Neurosyphilis

The syndromes of late stage NS generally appear between 5 and 25 years after initial infection. Late NS is much less common than early stage syndromes since the introduction of penicillin, but may be more likely in HIV-infected patients [1, 6, 35]. A recent study found that HIV-infected patients with a history of early or late NS had greater neurocognitive impairment than those without a history of syphilis [38]. Symptoms of NS can persist longer in HIV coinfected patients and occasionally have lasted up to a year after treatment, but presence of ART is associated with a shorter time to symptom resolution after therapy [39, 40].

Meningovascular syphilis usually occurs 5–12 years after infection, but can occur in early syphilis, and is caused by endarteritis involving the vessels of the central nervous system (CNS). The early symptoms of meningovascular syphilis are nonspecific and can include headache, vertigo, and insomnia [35]. However, there can be thrombosis and infarction involving the CNS vessels leading to sudden onset of symptoms including "syphilitic apoplexy." These symptoms (hemiplegia, hemianesthesia, homonymous hemianopsia, aphasia) are entirely dependent on the location of the lesion, which is usually the middle cerebral artery or its branches. Spinal vessels can also be involved leading to meningomyelitis with spastic paresis, sensory loss, or muscle atrophy.

Paretic NS (PNS), also referred to as general paralysis of the insane, general paresis, or dementia paralytica, is caused by active treponemal invasion of the CNS. In the pre-antibiotic era, up to 5% of syphilis infected patients would go on to develop PNS between 15 and 20 years after infection. Early symptoms include headache, irritability, forgetfulness, and personality change. Late symptoms include emotional lability,

impaired memory and judgment, confusion, delusions, mania, psychosis, delirium, and rarely seizures [35]. The classic Argyl Robertson pupil, in which the affected pupil accommodates but does not react to light, can occur as a late symptom but is more common in tabetic NS [35]. In paretic NS, there are signs of chronic meningitis on CSF analysis and classic atrophy of the frontal and temporal lobes, with sparing of the motor, sensory, and occipital cortices.

Tabetic NS, also referred to as tabes dorsalis or progressive locomotor ataxy, is due to involvement of the spinal cord leading to degeneration of the posterior roots and columns. In the pre-antibiotic era, approximately 3–9% of patients would develop this syndrome 20–25 years after infection. The syndrome is characterized by ataxic gait, paresthesias, bladder dysfunction, optic atrophy, Argyll Robertson pupil, diminished reflexes, impaired vibratory sense and proprioception, ocular palsies, and Charcot joints [6, 35]. CNS gummas can occur and cause space occupying lesions, but are extremely rare [1, 6, 35].

Tertiary Syphilis

Tertiary syphilis can affect any organ system; approximately a third of patients would go on to develop tertiary disease with an average onset 20–40 years after initial infection in the pre-antibiotic era. Tertiary syphilis can be divided into gummatous disease, cardiovascular syphilis, and late neurosyphilis discussed individually below [1, 6].

Gummatous Syphilis

Gummas are caused by a tissue destructive immune reaction to syphilis but have very few treponemes present in lesions. During early development, they are sometimes referred to as gummata prior to ulceration (Fig. 5.5a). Gummas (Fig. 5.5b) are characterized by granulomatous nodular lesions with variable central necrosis; they can develop as early as 2 years postinfection but usually occur much later. They usually affect the skin and skeleton but have been reported in the CNS, liver, heart, stomach, and upper respiratory tract. Unless they develop in vital organs, gummas are usually asymptomatic, benign, and resolve quickly with treatment [1, 6].

Cardiovascular Syphilis

The classic presentation of cardiovascular syphilis (CVS) is aortitis, caused by invasion of treponemes into the vasa vasora leading to obliterative endarteritis and fibrosis with patchy medial necrosis and destruction of elastic fibers. This process begins soon after the dissemination

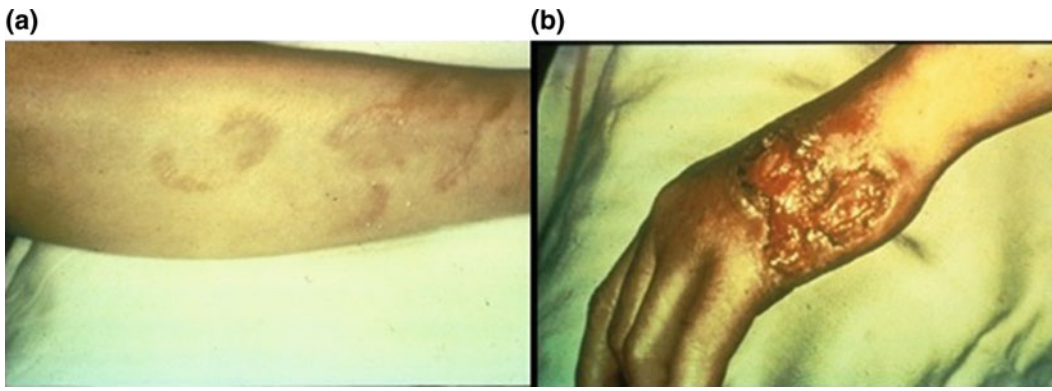

Fig. 5.5 **a** Serpiginous gummata. **b** Ulcerating gumma. Images obtained from http://www.cdc.gov/std/training/clinicalslides/powerpoint/syphilis.ppt

of treponemes after infection, and involves diffuse or focal weakening with increased risk of aortic root dilation and aneurysm formation [1, 6, 41]. On radiography, there may be a "tree-bark" appearance of the vascular intima and the "eggshell" appearance of the affected vessel. Aneurysms are usually single and saccular, but rarely can present as multiple or fusiform. The most common region for aortic aneurysm due to CVS is the ascending arch, but it can occur anywhere along the aorta.

Asymptomatic disease, found on autopsy or radiography, is the most common presentation of CVS, followed by aortic insufficiency (AI) which usually manifests between 10 and 30 years after infection and is associated with coronary ostial stenosis [41]. Coronary ostial stenosis is the second most common complication of CVS after AI. Coronary ostial stenosis often presents with angina, but rarely leads to MI due to slow progression over time allowing formation of collateral blood supply [41]. The least common complication of CVS is gummatous myocarditis which can present with myocardial infarction or conduction abnormalities [41].

Diagnostic Considerations

Despite major advances in treponemal antibody detection methods since the Wassermann test, the diagnosis of syphilis remains vexing to clinicians [7]. This is mostly due to our limited ability to study the organism in vitro; the diagnosis is further complicated by the protean nature of the disease and the complicated diagnostic criteria for disease staging (Table 5.2) [42, 43]. There are essentially two methods for syphilis diagnosis: direct detection and serology. It is important to note that the sensitivity of individual tests varies based on the stage of disease (Table 5.3) [44]. The diagnosis of syphilis in HIV patients is essentially identical to diagnosis in non-HIV-infected patients, but there are some specific concerns that are noted later in this section [45, 46].

Table 5.2 Clinical and laboratory criteria for diagnosis of syphilis (case definitions)[a]

Syphilis stage	Confirmed (requirements)	Probable (requirements)
Primary	(Requires 1 and 2 or 3)	(Requires 1 and 2 or 3)
	1. One or more chancres (ulcers) 2. Identification of *T. pallidum* in lesion exudate by microscopy 3. Detection of *T. pallidum* DNA in lesion exudate by PCR	1. One or more lesions compatible with chancres 2. Reactive nontreponemal test 3. Reactive treponemal test
Secondary	(Requires 1 and 2, 3, or 4)	(Requires 1 and 2)
	1. Localized or diffuse mucocutaneous lesions consistent with secondary syphilis a. Macular, papular, follicular, papulosquamous, or pustular rash b. Condylomata lata (anogenital region or mouth) c. Mucous patches (oropharynx or cervix) 2. Identification of *T. pallidum* in lesion exudates by microscopy (darkfield or DFA-TP) 3. Identification of treponemes in skin biopsy by silver, immunofluorescence (DFAT-TP) or immunohistochemical staining 4. Detection of *T. pallidum* DNA in tissue by PCR	1. Skin or mucous membrane lesions consistent with secondary syphilis 2. Reactive nontreponemal test titer ≥ 4 and a reactive confirmatory treponemal test

(continued)

Table 5.2 (continued)

Syphilis stage	Confirmed (requirements)	Probable (requirements)
Early latent	N/A	(Requires 1 and 2, 3, 4, 5 or 6) 1. Absence of signs and symptoms of syphilis 2. A reactive non-treponemal and treponemal test, and evidence of having acquired the disease within the preceding 12 months 3. A recent history of syphilis therapy for primary or secondary syphilis and a current non-treponemal test titer demonstrating fourfold or greater increase from the last non-treponemal test titer 4. Documented seroconversion or fourfold or greater increase in the non-treponemal test titer during the previous 12 months 5. A history of symptoms consistent with primary or secondary syphilis during the previous 12 months 6. Reactive non-treponemal and treponemal tests in a person whose only possible exposure occurred within the preceding 12 months
Late latent	Not applicable	(Requires 1 and 2) 1. Absence of signs and symptoms of syphilis 2. A reactive non-treponemal and treponemal test, and no evidence of having acquired the disease within the preceding 12 months
Late syphilis		
Benign (gummatous) and cardiovascular	(Requires 1 and 2 or 3) 1. Clinically compatible case (e.g., inflammatory lesions of the skin, bones, or cardiovascular system) 2. Identification of treponemes in tissue sections (usually skin biopsy) by silver, immunofluorescence (DFAT-TP) or immunohistochemical staining 3. Detection of *T. pallidum* DNA in tissue by PCR	(Requires 1, 2, and 3) 1. Clinically compatible case 2. A reactive serum treponemal test 3. Absence of clinical signs or symptoms consistent with neurosyphilis
Neurosyphilis	(Requires 1, 2 and 3, 4 or 5) 1. Clinical signs consistent with neurosyphilis 2. A reactive serum treponemal test 3. A reactive VDRL in CSF 4. Detection of *T. pallidum* DNA in CSF by PCR 5. Identification of treponemes in nervous system tissue by silver, immunofluorescence (DFAT-TP) or immunohistochemical staining	(Requires 1, 2, *and* 3) 1. Clinical signs consistent with neurosyphilis 2. A reactive serum treponemal test 3. Elevated CSF protein or leukocyte count in the absence of other known causes

[a]These criteria were modified from the 2014 Sexually Transmitted Diseases Surveillance Case Definitions for Nationally Notifiable Diseases

Direct Detection Methods

Direct detection for *T. pallidum* is performed via microscopy, fluorescent antibody detection, or polymerase chain reaction (PCR) (Tables 5.3 and 5.4). In darkfield microscopy, samples from exudative lesions (e.g., chancre, condyloma lata, secondary syphilis rash) (see Figs. 5.2, 5.3, and 5.4) are examined for spirochetes. It is important to note that this method cannot be used for oral lesions of syphilis because microscopy cannot distinguish between commensal oral spirochetes and *T. pallidum* [45]. Paraffin embedded tissue samples can also be examined using Direct Fluorescent Antibody (DFA) staining, silver staining, and immunohistochemical (IHC) staining to directly identify spirochetes. The touch prep DFA-TP can be used to examine dried exudate from clinical lesions or tissue preparations to detect pathogen as well [45]. Finally, PCR can be performed on tissue and blood samples to detect *T. pallidum*-specific DNA targets; however, PCR is not currently commercially available or FDA approved, although some laboratories have internally validated assays. It is notable that PCR performed on whole blood samples has poor sensitivity due to variation in spirochetemia during different stages of disease; PCR performed on direct clinical specimens (e.g., from lesions) is much more reliable [7, 45, 46]. Direct detection is the definitive and ideal way to diagnose syphilis infection, but these methods have limited utility during latent infection when most clinical diagnoses of syphilis are made from serologic testing [45].

Serologic Tests

There are a multitude of serologic tests available for the diagnosis of syphilis with varied sensitivities and specificities depending on disease stage (see Tables 5.3 and 5.4). These methods are generally characterized as treponemal or non-treponemal assays based on the type of antigen or antibodies that are detected.

Table 5.3 Common syphilis tests and their sensitivity and specificity [46]

Test	Type	Sensitivity primary (%)	Sensitivity secondary (%)	Sensitivity tertiary (%)	Specificity (%)
RPR	Non-treponemal	60–86	100	98	93–99
VDRL	Non-treponemal	67–78	96–100	85–95	96–99
TRUST	Non-treponemal	70–85	100	98	98–99
TP-PA	Treponemal	85–98	100	96–100	98–100
FTA-ABS	Treponemal	82–90	100	100	95–99
EIA/CIA tests	Treponemal	75–99	23–100	NA	94–100

Table 5.4 Types of syphilis tests and estimated number available commercially worldwide

Test type (examples)	Number available commercially
PCR	0
Flocculation (Non-treponemal tests)	4
Fluorescent antibody (FTA-ABS)	1
Hemagglutination (TP-PA)	3
EIA/CIA/multiplex flow (Trep-Check)	22
Rapid treponemal tests (Syphilis Health Check)	8
Rapid combination treponemal and non-treponemal tests (ChemiBio Dual Path)	2
Immunoblot (MarBlot)	3

Non-treponemal Tests

The original non-treponemal test was the Wassermann test, which detected a specific combination of lecithin, cardiolipin, and cholesterol thought to be released by human tissue upon invasion by *T. pallidum*. Modern non-treponemal tests have improved upon this assay but still detect a combination of the original three lipids in the Wassermann test. The most common non-treponemal tests used today are the Rapid Plasma Reagin (RPR) and the Venereal Disease Research Laboratory (VDRL) tests (see Tables 5.3 and 5.4) [6, 45]. These tests can be used to screen for syphilis, to monitor response to treatment, and help differentiate between untreated and treated infection [45]. Quantitative titers are thought to have some correlation with disease activity, and higher titers (e.g., $\geq$1:32) are typically observed in early syphilis. Positive results require confirmation with a treponemal-based assay since false positive non-treponemal tests can occur in association with several conditions including HIV, other chronic infections, autoimmune disease, heart disease, and pregnancy [46]. False negative non-treponemal test results can occur during early primary infection before antibody formation, which is usually considered 2 weeks from infection. The prozone effect can also occur when there is a false negative non-treponemal test from overwhelming antibody titers, especially in secondary syphilis, that interfere with the antigen-antibody flocculation on the test. In a prozone phenomenon, reactivity with undiluted serum is inhibited; therefore, most laboratories can avoid this phenomenon by testing diluted samples when a prozone reaction is suspected [39, 47, 48].

Other available non-treponemal tests are the Unheated Serum Reagin (USR) test (similar to RPR but microscopically read), and the Toludine Red Unheated Serum Test (TRUST) (also similar to RPR but uses a red dye marker) [46]. Dual Rapid Point of Care (POC) tests have also been developed that can provide immediate non-treponemal and treponemal antibody results, but these methods are not available in the US and are primarily used in resource-poor countries [49].

Treponemal Tests

Treponemal tests detect *T. pallidum* antigens or antibodies to the pathogen, and have been traditionally used as confirmatory assays for the non-treponemal-based tests. Treponemal tests have a higher sensitivity than non-treponemal tests in primary syphilis (see Tables 5.3 and 5.4), but will remain positive for life after initial infection. The treponemal-based detection methods can be grouped into fluorescent antibody tests, hemagglutination assays, enzyme-linked immunoassays (EIA), chemiluminescence immunoassays (CIA), immunochromatographic (usually used for Rapid Point of Care (POC) tests), immunoblot, and multiplex flow immunoassays (new technology similar to CIAs) [45].

Currently, the most commonly used tests are the Treponemal Pallidum Particle Agglutination (TP-PA) assay (hemagglutination assay), the Fluorescent Treponemal Antibody Absorption (FTA-ABS) test, and the various EIA/CIA tests that have recently been developed. Rapid POC treponemal-based tests are also growing in popularity, especially in resource-poor settings where they are used for screening purposes. Notably most of these tests, with the exception of immunoblot tests, will not distinguish between IgG and IgM so they cannot be used to differentiate between previously treated infection and current infection [45].

Diagnostic Algorithms

The traditional testing algorithm for syphilis involves a screening non-treponemal test (e.g., RPR), which requires a confirmatory treponemal test if reactive (e.g., TP-PA) (Fig. 5.6); this traditional algorithm is still recommended by the CDC for syphilis diagnosis [46]. However, the advent of automated CIA/EIAs has made it economically advantageous for larger laboratories to perform screening with treponemal tests in order to reduce laboratory labor and increase throughput of specimens. This is referred to as the reverse syphilis screening algorithm, in which a treponemal test is used for initial

screening followed by a non-treponemal test for positive results (see Fig. 5.6). The reverse algorithm requires that a second treponemal test be performed if there are discordant results (i.e., a positive treponemal test and a negative non-treponemal test), in order to help distinguish between a false positive treponemal test and true infection (either previously treated or active) [45, 50]. This second treponemal test should have comparable sensitivity to the initial treponemal test; therefore, the CDC recommends that TP-PA be used for confirmatory testing if there are discordant results in the reverse algorithm [46, 51]. If the second treponemal test is positive, then the clinician should treat for syphilis unless there is documentation of prior treated syphilis [46]. If the second treponemal test is negative, a false positive initial treponemal test is likely but the clinician should decide whether further action is warranted based on clinical and epidemiologic considerations.

A third syphilis screening algorithm is recommended by the European Center for Disease Prevention and Control (ECDC), using an initial treponemal test like an EIA followed by a second confirmatory treponemal test (e.g., TP-PA) if the first test is positive. This method disregards the non-treponemal tests for diagnosis but uses them for monitoring of treatment response [52, 53]. The three syphilis algorithms have been evaluated for differences in sensitivity and specificity, demonstrating that the traditional algorithm has a lower sensitivity (75.8%) in high prevalence settings compared to the reverse algorithm or the ECDC algorithm (>99%) [52, 53]. However, another study found that the traditional and reverse algorithms identified and treated the same number of cases [54, 55]. Another consideration is costs, since the reverse algorithm has been found to be slightly more costly overall due to increased number of confirmatory tests, patient follow -up, and over-treatment [54, 55].

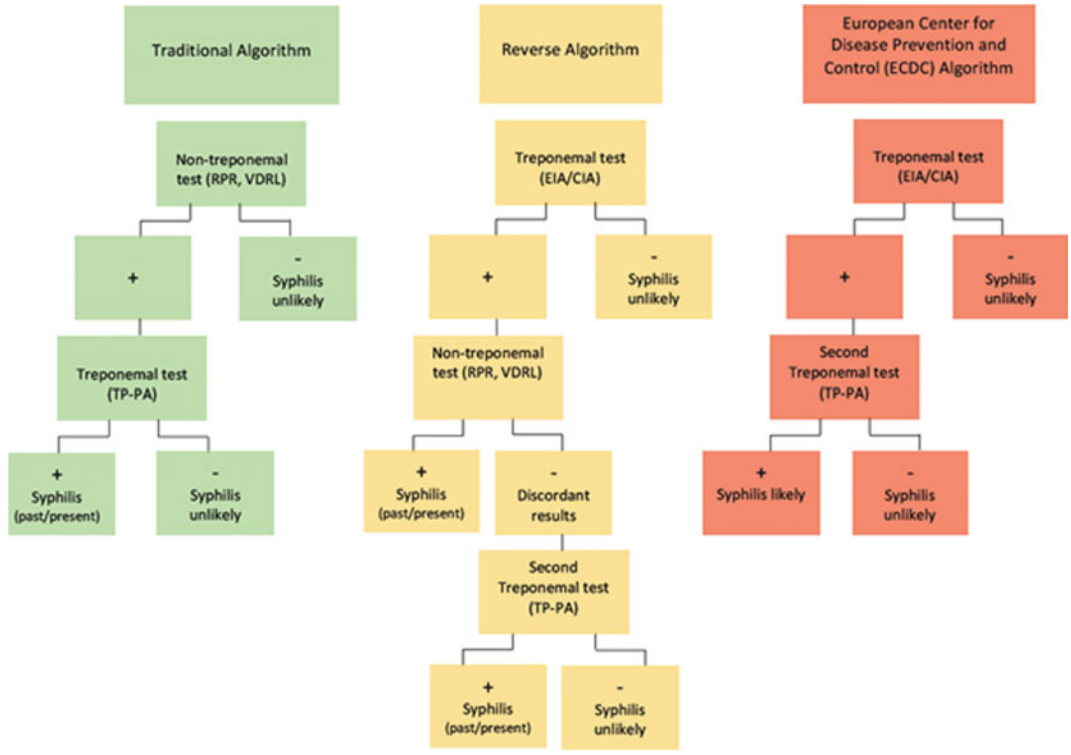

Fig. 5.6 The different syphilis screening algorithms used in clinical laboratories. Adapted from Tong et al. [53], by permission of Oxford University Press

Therefore, each clinic and laboratory should consider their population prevalence of syphilis, laboratory resources, and patient compliance with follow-up testing when deciding which testing algorithm to implement [52].

Neurosyphilis Diagnosis

The diagnosis of neurosyphilis requires lumbar puncture with evaluation of a CSF non-treponemal test, cell count and protein and should be performed in all patients with neurologic signs and symptoms, including ocular and auditory complaints. The diagnosis can be difficult to make due to the limitations of the CSF markers for syphilis, especially in asymptomatic individuals who undergo lumbar puncture due to serologic treatment failure or HIV-infected patients. The diagnosis of neurosyphilis in HIV-negative patients is typically made based on a positive CSF VDRL, CSF pleocytosis >5 cells, and/or elevated CSF protein [35, 45, 46, 52]. There are similar diagnostic criteria for HIV-infected patients, but a higher CSF pleocytosis of >10–20 cells is required since HIV infection alone can cause a mild CSF WBC elevation [35, 46]. Some experts feel providers should have a low threshold to perform a neurologic evaluation among HIV coinfected patients with an RPR titer $\geq$1:32 and/or CD4 count $\leq$350, as these factors have been associated with neurosyphilis in the HIV-infected population. However, the long term benefit of this approach is not known at this time [45, 52, 56].

The CSF VDRL provides the definitive diagnosis of neurosyphilis, but has a sensitivity of only 67% and specificity of 90%. An FTA-ABS can be performed when the CSF VDRL is negative due to its higher sensitivity; however, it has low specificity due to the fact that IgG can cross the blood–brain barrier and due to these test parameters it is most useful to help exclude neurosyphilis [45]. CSF RPR is not recommended since it has a significantly lower sensitivity than the CSF VDRL [21]. Interestingly, Marra et al. [57] demonstrated that the chemokine CXCL13 is elevated in the CSF of patients with symptomatic and ANS independent of pleocytosis or elevation in protein; however, further studies are needed in order to determine the role of this marker in future diagnosis of neurosyphilis.

Special Diagnostic Considerations in HIV Coinfection

In general, syphilis diagnosis in HIV coinfected patients is similar to diagnosis in HIV-negative patients, but there are a few differences that clinicians should be aware of. Most notably, syphilis screening for sexually active HIV patients should be performed at entry into care, at least yearly, and as often as every 3–6 months in HIV-infected MSM engaging in sexual risk behaviors due to their higher likelihood of coinfections [46, 58]. As mentioned previously, the presence of HIV infection can cause false positive non-treponemal tests; however this is considered rare and the possibility of coinfection is more likely [45]. HIV coinfected patients may have higher non-treponemal antibody titers than other patients, which can theoretically lead to a higher incidence of the prozone effect. Finally, HIV coinfected patients may have a higher risk of treatment failure, serologic nonresponse, and reinfection, which will be discussed further in the section below [39, 45].

Treatment

Penicillin has been the preferred treatment for syphilis since the 1940s, and is considered to be highly effective [46, 59]. The treatment of syphilis in HIV-infected patients is generally the same as for HIV-negative persons; however, there are some nuances and areas of debate about syphilis therapy when managing an HIV coinfected patient. Furthermore, there are additional concerns regarding serological outcomes after treatment that can be more problematic in coinfected patients.

Treatment for Primary, Secondary, Early Latent Syphilis

The treatment of early syphilis without CNS involvement is 2.4 million units of benzathine penicillin G, which is usually split into two intramuscular injections (IM) (Table 5.5) [46]. Despite this recommendation, there are many providers who advocate for extended courses of therapy, usually one or two additional administrations of 2.4 million units of benzathine penicillin G IM one week apart, in HIV coinfected patients due to the epidemiologic studies which have shown higher rates of treatment failure, neurosyphilis, and slower response rates in this population [39, 59–63]. Currently, the CDC does not recommend extended therapy for HIV coinfected individuals; however, this is an area of active debate and experts in the field have stated that it is unlikely to be resolved until we have better diagnostic techniques for syphilis [63]. There have been studies examining this question which have found no significant differences in outcome with extended courses of penicillin in HIV coinfected patients; however, there is a lack of randomized controlled trial data and these prior studies have definite limitations (see Table 5.5) [43, 59, 62, 63].

Alternative treatment regimens for early syphilis include doxycycline/tetracycline, ceftriaxone, and azithromycin (see Table 5.5), which are reserved for nonpregnant patients with

Table 5.5 Syphilis treatment by stage

Syphilis stage	Primary therapy	Alternative therapy	Follow-up
Early syphilis (primary, secondary)	BPG, 2.4 MU IM × 1 dose	Doxycycline 100 mg po BID × 14 d	Non-HIV: clinical and serologic examination at 6 and 12 months
		Tetracycline 500 mg po QID for 14 days	HIV: clinical and serologic follow-up at 3,6,9,12, and 24 months[a]
		Ceftriaxone 1-2 g/d IM or IV for 10–14 d[b]	
Early latent syphilis	BPG, 2.4 MU IM × 1 dose	Same as primary and secondary	Same as late latent
Late latent syphilis	BPG, 2.4 MU IM × 3 weekly doses	Doxycycline 100 mg po BID × 28 days	Non-HIV: non-treponemal serologic testing at 6, 12, and 24 months
		Tetracycline 500 mg po QID for 28 days	HIV: clinical and serologic follow-up at 6,12, 18, and 24 months[a]
Tertiary syphilis (cardiovascular and gummatous)	BPG, 2.4 MU IM × 3 weekly doses	None	Same as latent syphilis, CSF exam should be performed to rule out NS prior to initiation of therapy
Neurosyphilis	Aqueous penicillin G, 18-24 MU/d IV (3–4 MU IV every 4 h or as continuous infusion) × 14 d; some practitioners would follow treatment with 1–3 extra doses of BPG, 2.4 MU IM at weekly intervals	Procaine penicillin, 2.4 MU/d IM, plus probenecid 500 mg po QID × 10–14 d	HIV and non-HIV: repeat CSF analysis every 6 months until cell count is normal if pleocytosis initially present + clinical and serologic exams as above
		Ceftriaxone 2 g/d IM or IV × 10–14 d	

Abbreviations: *BPG* benzathine penicillin G; *HIV* human immunodeficiency virus; *MU* million units; *IM* intramuscular; *BID* twice daily; *QID* four times daily; *IV* intravenous; *po* orally

[a]If inadequate response to therapy clinically or serologically CSF examination indicated

[b]Dose and duration are not clear due to lack of data for this regimen

penicillin allergy or for persons in resource limited settings, Doxycycline and tetracycline have limited evidence as treatment regimens for syphilis (see Table 5.5) but have been used successfully for many years. Studies have shown no difference in outcomes between penicillin versus doxycycline [64], although studies of HIV coinfected patients have demonstrated 73–89% serologic response rates for the latter [46, 59, 64]. The optimal ceftriaxone dosing has not been established, but there is some evidence for 1–2 g given intramuscularly or intravenously daily for 10–14 days as an alternative regimen for early syphilis. However, response rates as low as 65% have been observed with ceftriaxone in HIV coinfected patients [46, 59, 65, 66]. Although azithromycin has been shown to be effective at a single oral dose of 2 g, resistance is becoming increasingly common; thus, this regimen should only be considered when penicillin or doxycycline therapy is not feasible and should be avoided as an alternative therapy among HIV-infected individuals or MSM [43, 46, 59, 67–70].

Neurosyphilis

Neurosyphilis (including ocular syphilis) occurring at any time during disease course, early or late, should be treated with 18–24 million units of aqueous crystalline penicillin G per day for 10–14 days, administered as 3–4 million units intravenously every 4 h or as a continuous infusion. Alternative regimens are procaine penicillin plus probenecid and ceftriaxone (see Table 5.5), but are both considered suboptimal [46]. Extremely limited data suggest ceftriaxone 2 g daily intramuscularly or intravenously for 10–14 days may be effective for neurosyphilis, although this is likely less effective in HIV coinfected patients [46, 59]. Given that the duration of treatment for neurosyphilis is less than that for late stage syphilis, some providers advocate for one to three additional doses of 2.4 million units of benzathine penicillin G administered weekly after completion of neurosyphilis treatment [16, 46, 59].

Late Syphilis

Late latent syphilis (initial infection greater than 1 year prior) and tertiary (cardiovascular or gummatous) syphilis should be treated with 7.2 million units of benzathine penicillin G intramuscularly divided into three equal doses given weekly for three consecutive weeks [46]. The only acceptable alternative regimen for late latent syphilis is doxycycline/tetracycline (see Table 5.5). There are no alternative treatment regimens for tertiary syphilis and individuals with tertiary syphilis should undergo a lumbar puncture to rule out neurologic involvement and the need for intravenous therapy. Missed doses of IM penicillin are not optimal but can be tolerated at intervals up to 14 days, with an optimal dosing interval of 7–9 days. If the interval is greater than 14 days between doses, then the entire treatment regimen should be restarted. Missed doses are not acceptable in the setting of pregnancy and the regimen should be restarted if any dose is missed [46].

Jarisch–Herxheimer Reaction

The Jarisch–Herxheimer reaction is an acute febrile reaction that occurs with treatment of syphilis, due to release of bacterial endotoxins and microbial antigens. While it is most common after treatment of early syphilis, likely due to increased treponemal burden, it can occur at any stage during therapy [46]. This reaction has been found to be slightly more common in HIV coinfected patients [71]. Although this reaction may occur in pregnant patients and may induce labor, this possibility should not delay treatment which is important to prevent congenital syphilis [46].

Additional Work up and Education

All patients who are HIV-negative or have unknown HIV status and are diagnosed with syphilis should be tested for HIV coinfection and have retesting at 3 months, especially among those with a high prevalence of HIV infection

(e.g., MSM) [46]. Patients, especially HIV coinfected patients, should be educated about their risks for reinfection, and advised to refrain from unprotected sexual contact until resolution of signs/symptoms (for those with primary or secondary syphilis), or up to 2 weeks to prevent further transmission [46].

Management of Sex Partners

Prompt attention should be paid to the sex partners of a patient diagnosed with syphilis given its high rate of transmission. Notification should be provided to sexual partners in the last 3 months, 6 months, and 1 year for those with primary, secondary and early latent syphilis, respectively [46]. Anyone who is a sexual contact to a patient diagnosed with primary, secondary, or early latent syphilis in the preceding 90 days should be treated presumptively regardless of syphilis testing results, due to the possibility of incubating syphilis. If sexual contact was greater than 90 days prior to diagnosis, a stat non-treponemal test should be performed and the treatment decision should be based on testing results and history. If test results are not readily available and follow-up is uncertain, empiric therapy should be strongly considered. In some areas with a high prevalence of syphilis, presumptive treatment of partners to late latent syphilis is performed, especially if the index patient has a high non-treponemal titer (>1:32) [46].

Monitoring/Follow-Up

Clinical monitoring and repeat non-treponemal titers are recommended for all patients after treatment of syphilis to ensure an appropriate response to therapy. In HIV coinfected individuals, the recommendations for follow-up is intensified due to possible increased risk of treatment failure, reinfection, or underlying undiagnosed neurosyphilis. Evaluation and repeat serological monitoring after therapy for HIV-coinfected patients is recommended at 3, 6, 9, 12, and 24 months for early syphilis, and 6, 12, 18, and 24 months for late syphilis [46]. If treating for neurosyphilis in the setting of an initial pleocytosis on CSF examination, repeat CSF examinations should be performed every six months until normal; if CSF leukocyte count fails to normalize after 2 years, retreatment should be considered [46].

Treatment failure and reinfection can be extremely difficult to distinguish clinically and are impossible to distinguish by serology [46, 66]. These conditions are indicated by persistence or recurrence of signs and/or symptoms, or a sustained (greater than 2 weeks) $\geq$ fourfold rise in non-treponemal titers from baseline titers. When considering these conditions, clinicians should obtain a careful history and examination to guide retreatment regimens. In HIV coinfected patients, CSF analysis is likely indicated if treatment failure is suspected to rule out neurosyphilis even in the absence of symptoms [46, 59, 66].

Serological Nonresponse and the Serofast State

Most patients will achieve a fourfold decline in non-treponemal antibody titers within 6–12 months after treatment, but some patients will have less than a fourfold decline in titers (serological nonresponse) or low-level titers that persist over time (serofast state). A recent review found that a substantial proportion (12.1%) of patients will exhibit serological nonresponse after treatment [72]. The serofast state can occur in up to 20% of patients [43, 46, 59, 66]. HIV coinfected patients are more likely to remain serofast and have fluctuations in non-treponemal titers during follow-up [43, 46, 59]. Retreatment has been shown to have only modest effects on reducing non-treponemal titers in the serofast state, and it is unclear how to manage this clinically [46, 59, 66]. Risk factors for remaining serofast include lower baseline RPR (<1:32), older age (>30), and later stage of syphilis [43].

Special Considerations with HIV Coinfection

HIV-infected patients are generally provided the same treatment regimens for syphilis as HIV-uninfected patients. However, there are some considerations in management of HIV-coinfected patients that clinicians should be aware of, including reduced efficacy of alternative antibiotic regimens, the need for more intensive clinical and serological follow-up, the increased risk of treatment failure/reinfection, and the concern about early symptomatic and ANS. A low CD4 count (<200) in HIV-infected patients has been associated with treatment failures and increased risk of spirochetemia; inversely, the presence of anti-retroviral therapy has been associated with a 60% decrease in risk of treatment failure and decreased risk of neurosyphilis [16, 65, 73]. One study reported that 60% of HIV coinfected patients did not receive follow-up non-treponemal titers after therapy; however, this is extremely important given the increasing prevalence of coinfections, increased risk of morbidity, and up to four times greater risk of serological treatment failure in this population [39].

Special Situations: Pregnancy and Penicillin Allergy

Penicillin is the only recommended treatment of syphilis in the HIV-infected or HIV-uninfected pregnant patient. Many practitioners give an extra dose of penicillin at 1 week after initial treatment for early syphilis. Missed doses of penicillin in pregnancy (i.e., for late latent infection) are not acceptable and any missed dose requires restarting the treatment regimen [46].

In the event of a penicillin allergy, pregnant women should be desensitized to penicillin in the appropriate environment and given treatment appropriate for their stage in consultation with an allergist and a maternal fetal medicine specialist if possible. If treatment occurs in the second half of pregnancy, there is an increased risk of premature labor from a Jarisch–Herxheimer reaction; however, this risk should not delay treatment and all pregnant women requiring syphilis therapy should be advised to report to their obstetrician immediately if they experience fever, contractions, or decreased fetal movement. After syphilis therapy, close follow-up with repeat titers at 28–32 weeks and delivery or up to monthly for high-risk patients are indicated, as well as consideration of pathologic examination of the placenta and umbilical cord for treponemes after delivery. For HIV coinfected pregnant women, placental inflammation from congenital infection may increase risk for vertical transmission of HIV [46].

Congenital syphilis, although an extremely important entity and the most significant infectious disease affecting fetuses and newborns worldwide, will not be discussed in this chapter. For further information on this topic, please refer to the CDC 2015 STD treatment guidelines [14, 46].

Vaccines

There are currently no vaccines for syphilis, although complete protection has been achieved in a rabbit model using an extended immunization regimen of gamma irradiated *T. pallidum* [14]. Research is ongoing into vaccine development, which would be an important public health achievement given the increasing incidence of adult syphilis and the continued impact of congenital syphilis worldwide. Unfortunately, progress has been limited by lack of personnel, research funding, and large market gaps; development of a vaccine in the foreseeable future is unlikely [14].

Conclusions

Despite being one of the oldest known infections, syphilis is one of the least well understood human diseases and one of the most difficult to diagnose and manage. Despite having effective and relatively inexpensive treatments, syphilis incidence is increasing worldwide. Currently,

there is a worldwide epidemic of syphilis in the MSM and HIV-infected communities. This is particularly problematic given the synergistic relationship between HIV and syphilis which allows for increased HIV transmission. If the syphilis epidemic continues unabated, it is feasible that we will see a significant increase in HIV incidence which will likely spread beyond the currently afflicted communities. Syphilis prevention is critical to both HIV-infected and uninfected populations. Clinicians should be familiar with the diagnosis and management of syphilis among HIV-coinfected patients, and scientists should focus on investigations with *T. pallidum* in order to improve diagnostics, clinical practice, and future preventive strategies including vaccination.

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Herpes Simplex Virus Infections

6

Peter A. Leone

Introduction

Human immunodeficiency virus type 1 (HIV-1) and herpes simplex virus (HSV-2) have a synergistic relationship. HIV-1 exacerbates the clinical manifestations of HSV-2 both in terms of frequency of outbreaks and shedding of virus. HSV-2 infection increases the risk of HIV acquisition and transmission. The unrecognized high rates of HIV/HSV-2 co-infection and the primarily asymptomatic reactivation of HSV-2 are instrumental in HSV-2 infection being under diagnosed in HIV-infected individuals, and clinical management not being initiated. As such, unrecognized and untreated genital HSV-2 infection contributes to the transmission of both infections.

Basic Science Concepts

Primary HSV infection occurs at the mucosal site of inoculation with retrograde infection of sensory nerve ganglia. Following resolution of primary infection, HSV enters a latent state in the sensory nerve ganglia and can reactivate to cause active disease at any mucosal site innervated by the infected ganglia.

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During primary HSV infection, natural killer (NK) cells are important effectors of immunity. NK cell activation depends on the production of several cytokines that have direct and indirect effects important in limiting viral replication. As the immune response matures, clearance of HSV from infected tissues is T cell mediated and involves cytokine-mediated effector mechanisms and direct cytolysis of virus-infected cells. Both CD4+ and CD8+ T cells are important in resolution of infection [1, 2].

HIV induced deficits in host innate or cellular immunity result in more frequent disease manifestations, which can be persistent ulcerations or disseminated infection. Persistent HSV-2 is a common presentation of advanced HIV-1 infection where low CD4 counts and high viral load are associated with increased frequency of HSV-2 shedding [3, 4].

The efficiency of the immune response appears to influence the quantity of virus-established latency in the ganglia. The elements that contribute to this control are not completely known, but interferon gamma is likely to be important. Initial evidence suggests that immune response may play a supplemental role in maintaining latency of HSV but this remains to be confirmed. Studies have changed the understanding of HSV-2 infection away from an outbreak focused disease to a continuum infection. Reactivation of virus in the dorsal root ganglion is frequent with median shedding rates of 25% of days based on once a day swabbing of the genital tract for HSV detection by PCR. More recent studies suggest prior

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studies underestimated the frequency of shedding. Swabbing of the genital tract for HSV detection every 6 h found 49% of viral shedding events lasting less than 12 h and 29% lasting less than 6 h. In essence, viral reactivation is nearly constant and produces local inflammation at the site of the genital mucosa. This local inflammatory response is believed to be responsible for the increased risk of HIV-1 acquisition among HSV-2 seropositive women (relative risk (RR) = 3.4; 95% CI 2.4, 4.8), men (RR = 2.8; 95% CI: 2.1, 3.7), and MSM (RR = 1.6; 95% CI:1.2, 4.8) [5–7].

Case

A 34-year-old female is referred to the STD clinic for diffuse chronic ulceration over her labia. She had been seen in a local emergency department and was given a prescription for TMP-SMX for 5 days and mupirocin ointment to be applied TID. She said the ulcerations had started 8 weeks prior to being seen and had extended from her left labial area to involve her entire vulva and vaginal introitus. She reports no previous history of genital ulcer disease. She is widowed for two years with her husband having died in a work-related accident. She has not engaged in sexual intercourse since her husband's death, gives no history of sexually transmitted infections (STIs), and has never been tested for HIV. Physical exam reveals a thin adult who is in a moderate amount of pain. She was found to have complete denuding of epithelium over her entire vulva and labial area. She was admitted to the hospital and presumptively started on acyclovir 10 mg/kg q 8 h. HSV PCR from the labial area was positive for HSV-2 and her HIV test was positive. She was found to have a CD4 count of 23 cells/mm^3. Over a 3–4-day period her lesions began to crust over. She was switched to valacyclovir 1000 mg PO BID until her lesions healed over and started on antiretroviral therapy (ART) for her HIV. Over a 4-week period her lesions completely healed.

Epidemiology

HSV-2 is the most common cause of genital ulcer disease. It is estimated that 16% of the world's population age 15–49 years are infected with HSV-2. Seroprevalence of HSV-2 varies geographically and by gender, age, and HIV serostatus. The highest rates reported are in sub-Saharan Africa with seropositive rates for HSV-2 in the general population ranging from 30 to 80% in women and 10–50% in men. Seroprevalence estimates are more readily available for women and range from 20 to 40% for women in Central and South America [8–10].

The incidence of new HSV-2 infections in the US is estimated at greater than 1.5 million cases annually. HSV-2 infection, which is extremely rare under the age of 12, rises sharply with the onset of sexual activity, and peaks by the early 40 s. The seroprevalence of HSV-2 infection rose 30% between 1978 and 1991 to 21.7%. The national seroprevalence estimates in 1999–2004 decreased to 17%. The decrease was primarily seen in persons 14–18 years of age. The majority of individuals with genital HSV infection have undiagnosed initial infections and unrecognized recurrent outbreaks [11].

HIV-infected individuals have higher rates of HSV-2 infection relative to those who are HIV uninfected with an estimated 85% of HIV-1 infected individuals being HSV-2 seropositive in sub-Saharan Africa and 65–90% of MSM with HIV in the US [12, 13].

Clinical Presentation

Genital infection with HSV is classified into five categories: (1) Primary first episode, (2) Non-primary first episode, (3) First recognized episode, (4) Recurrent episode, and (5) Subclinical shedding. The primary first episode refers to infection with either HSV-1 or HSV-2 in an individual who has never been infected with a HSV. In immunocompetent hosts, this event usually goes unrecognized. After an

incubation period of 1–14 days (average, 4 days), a papule appears that evolves into a vesicle within 24 h (Fig. 6.1). These vesicles can be clear or pustular and rapidly evolve into shallow, nonindurated, painful ulcers. Clinical associations include dysuria, inguinal lymphadenitis, vaginal discharge, and cervicitis. Systemic symptoms, including myalgia, malaise, fever, and other flu-like symptoms, may also develop. Crops of lesions occur over 1–2 weeks. Crusting and healing require an additional 1–2 weeks (Fig. 6.2) [14].

A non-primary first episode is an infection in an individual who has had a previous infection with either HSV type, typically a previous orolabial infection with HSV-1, in whom a genital HSV-2 infection develops. Generally, it is less severe than the primary first episode due to a partial humoral and cellular immune response. There are fewer lesions, less pain, fewer systemic symptoms, and more rapid resolution of lesions (usually 5–7 days). This episode is clinically similar to that of recurrent disease and can be mistaken for recurrent infection [14, 15].

A first recognized episode is an initial clinical presentation of infection whether it is a first episode or recurrent infection. Clinical presentation is an unreliable means for distinguishing incident infection from recurrent disease and there is little clinical utility in making this distinction. This is particularly true in HIV-infected individuals, since frequency and severity of outbreaks is inversely correlated with CD4 count [7, 8, 14].

A recurrent episode is the second or subsequent episode of genital herpes with the same virus type. HSV-2 accounts for more than 90% of recurrent genital herpes. The median number of recurrences per year in immunocompetent individuals is 4 with 38% of individuals having 6

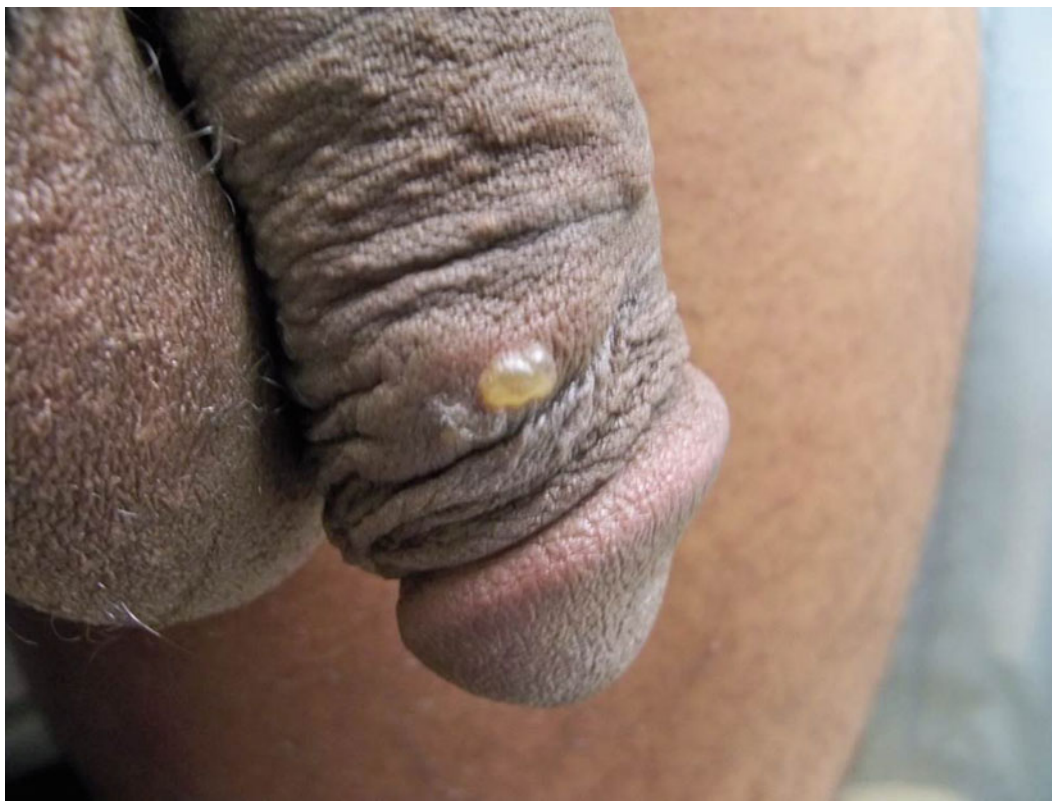

Fig. 6.1 Vesicle secondary to HSV. *Note* Small papules proximal to the vesicle

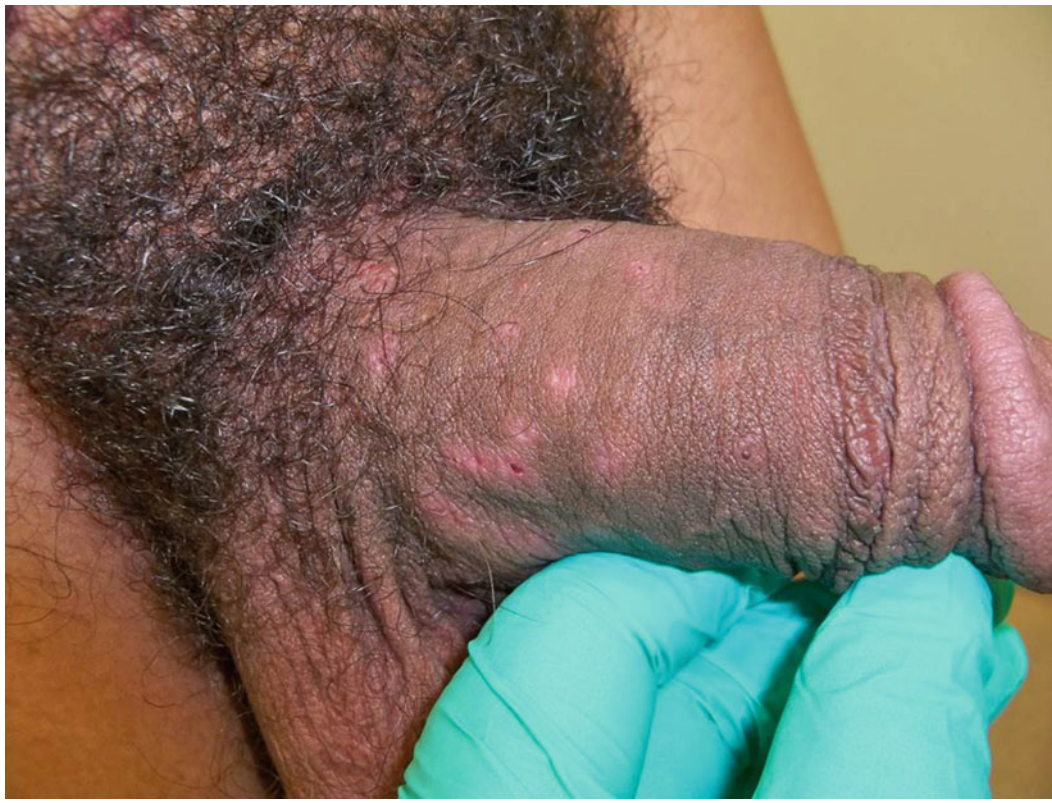

Fig. 6.2 Healing lesions due to primary infection with HSV-1

or more recurrences annually. Recurrent outbreaks are usually not associated with systemic symptoms, and are fairly mild and often go unrecognized, but may be preceded by a prodrome of paresthesia or dysesthesia. A cluster of localized vesiculopustular or ulcerative lesions develops and tends to lateralize to one side of the midline (Fig. 6.3). "Atypical" lesions are common and may be mistaken for excoriation or irritation (Fig. 6.4). Predominant locations of lesions are the glans or shaft of the penis in men, the vaginal introitus or labia in women, and the buttocks and anal area in both sexes. A neuropathic prodrome may occur 6–24 h before the appearance of lesions [14].

Subclinical shedding refers to the detection of virus in the absence of visible lesions. Our understanding of genital herpes has shifted from that of intermittent outbreaks to one of low-grade continuous shedding of virus that can be detected by viral culture of the genitals and anus 5–7% of days and 15–20% of days by polymerase chain reaction (PCR) [14, 16]. The frequency of subclinical shedding is greatest the first 6–12 months after acquiring genital herpes. In HSV-2, subclinical shedding occurs in virtually all individuals but is more common in women and diminishes in frequency over time. Many episodes are temporally associated around clinically recognized outbreaks, with virus detected one to several days preceding or following resolution of lesions. The development of symptoms and/or lesions appears to be most related to duration of viral shedding and not the host immune response in HIV-uninfected individuals; but, as evidenced in advanced HIV, CD4 cells are critical for controlling mucosal shedding of HSV-2. Patients who are counseled about the mild signs and symptoms of recurrent outbreaks may learn to recognize some periods when they

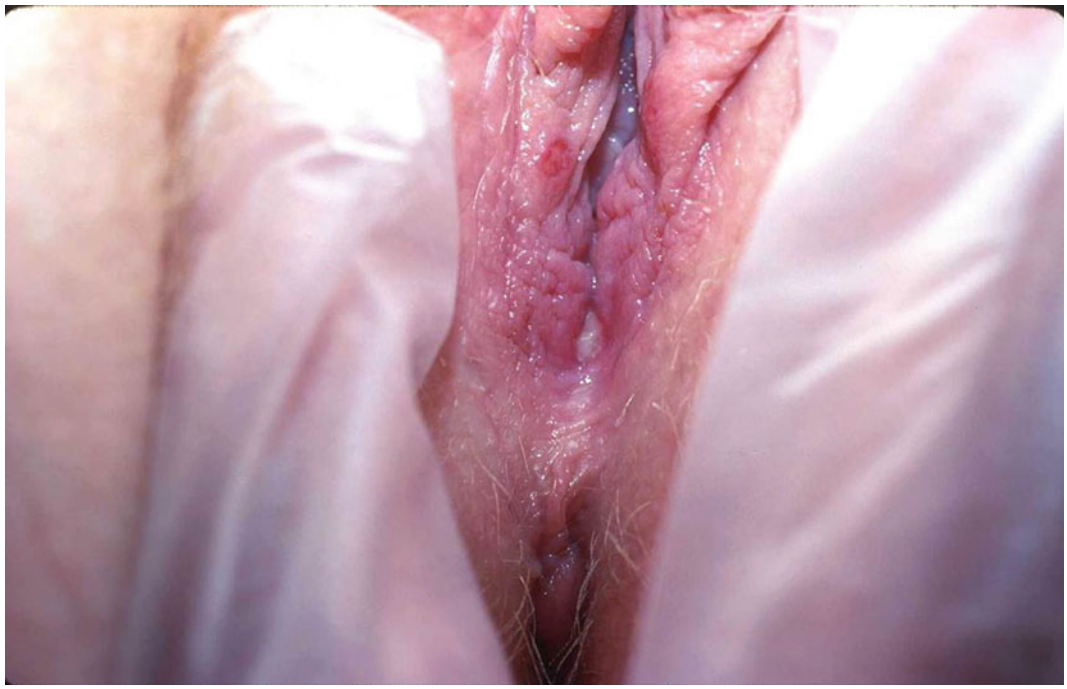

Fig. 6.3 Recurrent genital herpes

are at risk of transmitting HSV to partners. Unfortunately, because up to 70% of transmission is attributable to asymptomatic viral shedding, patients are potentially infectious to all sexual partners regardless of signs or symptoms. The higher rates of asymptomatic shedding in HIV can lead to higher rates of transmission of HSV-2 to sexual partners.

Like HIV-uninfected individuals, most HIV-infected persons with HSV-2 infection are asymptomatic and have unrecognized HSV-2 infection. There is a correlation of stage of HIV infection with the rate of HSV-2 reactivation but all HIV-infected individuals will shed HSV-2 asymptomatically from the genital tract. The frequency of shedding of HSV-2 and quantity of shedding are higher among HIV-infected persons with lower CD4 counts. Initiation of ART can increase the prevalence of genital ulcers and HSV-2 shedding for the first 3 months after ART, with a return to baseline after 6 months of ART. Increased shedding and genital ulcer disease is believed to be due to immune reconstitution inflammatory syndrome (IRIS) which has been seen with other herpes family infections, such as human herpes virus-8 (the etiology of Kaposi sarcoma), cytomegalovirus and varicella zoster virus [17].

The clinical course of HSV-2 in HIV-infected individuals can vary greatly but can be associated with more frequent and prolonged outbreaks at multiple anatomic sites. Lesions can be atypical in appearance and deeply ulcerative. This is typically seen in individuals with very low CD4 counts and can lead to misdiagnosis. Disseminated disease can include esophagitis, meningoencephalitis, retinal disease, and hepatitis but is rarely seen in even advanced HIV infection [18].

Atypical clinical presentations of HSV disease may be observed in HIV-infected individuals [18–20]. These relatively rare clinical presentations may be vegetative, hypertrophic, pseudotumoral features with or without ulcerations and may be misdiagnosed (Fig. 6.5) [21–23]. The pseudotumoral forms of anogenital HSV-2 may mimic epidermoid carcinoma or lymphoma in appearance. Reported cases suggest a poor

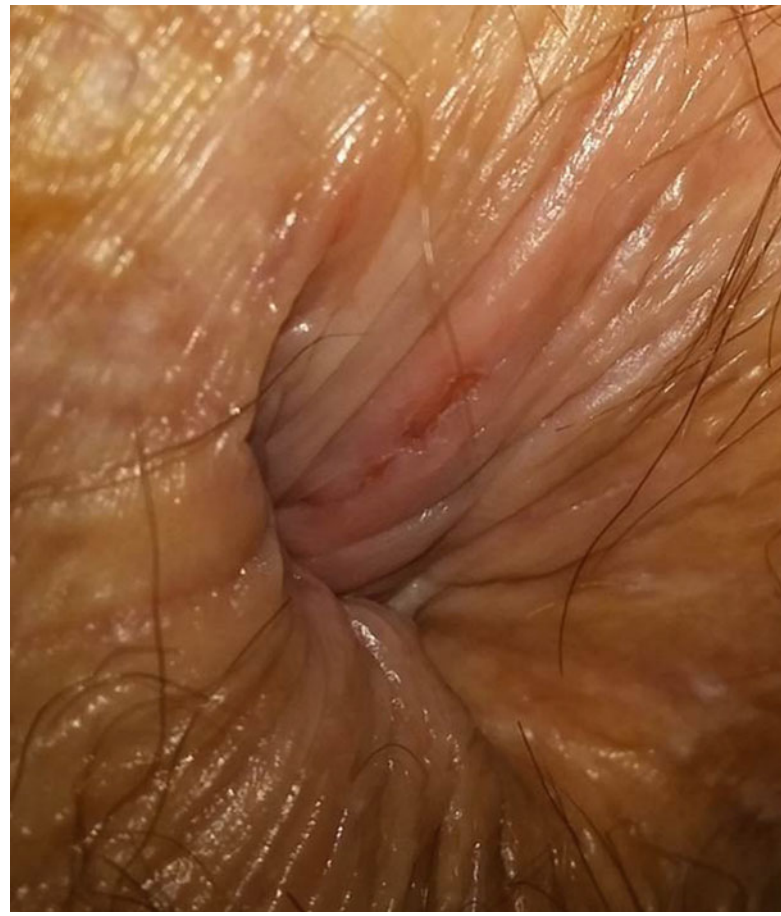

Fig. 6.4 Anal herpes lesion

response to treatment with ACV and these lesions have been associated with the emergence of drug-resistant virus subtypes though the role of viral resistance to ACV and to other antiviral drugs such as foscarnet and cidofovir has not been established [21–24]. Biopsies of lesions demonstrate the predominance of polyclonal lymphoplasmocytic.

B cells among the cellular lesional infiltrate and suggest these lesions may represent an immunoreconsitution response supporting the hypothesis of a dysregulated antigen-driven immune reaction directed toward HSV-2 derived antigens. The lack of response to therapy may be due to poor penetration of drug into the tissue. Clinical response has been found using topical imiquimod and provides support that an immune stimulus targeting innate immunity may overcome the deficiency of antiherpetic immunity that persists despite HAART-induced immune recovery [21].

Differential Diagnosis

Discrete genital or anal ulcers in sexually active young adults have a relatively narrow differential diagnosis. Chancroid is rare in the United States, while syphilis, which had been at an historic low, has rapidly increased within MSM populations. In particular, syphilis and HIV co-infection is now found in over 50% of all newly diagnosed syphilis infections in the United States.

The differential diagnosis should include the following infectious etiologies: genital herpes, syphilis, chancroid, primary human immunodeficiency virus (HIV), lymphogranuloma venereum, and donovanosis.

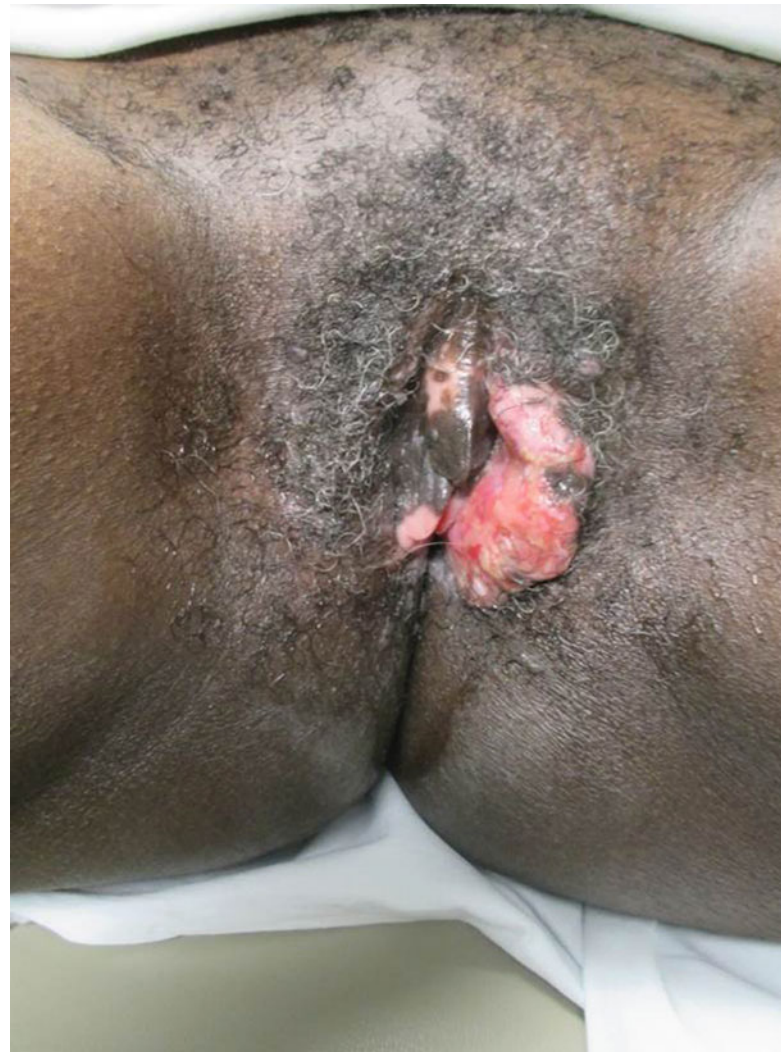

Fig. 6.5 HIV-infected female with acyclovir-resistant HSV

Primary syphilis may be distinguished from other ulcers by the presence of a nontender, indurated, nonpurulent ulcer. Other ulcer characteristics are not helpful in distinguishing infectious etiologies, but are more likely to be due to herpes. Diagnostic testing is critical to prevent a missed diagnosis of genital herpes for any genital ulcer.

Diagnostic Approach

Viral culture had been the "gold standard" for the diagnosis of genital herpes. Nucleic acid amplification tests (NAAT) for HSV DNA is 3–4 times more sensitive than viral culture and has been shown to increase viral detection from genital lesions by 11 to 70% compared to cell culture. Although NAATs are offered by many reference laboratories, not all are FDA approved. Viral detection methods, whether culture or NAATs, allow the etiologic diagnosis of a genital ulcer. NAATs are still generally more expensive than HSV cultures but the costs are decreasing and approaching that of culture. They also permit distinction of HSV-1 from HSV-2, an important consideration for prognosis and counseling since genital HSV-1 infection is less likely to be shed or cause outbreaks than genital HSV-2 infection. Cultures are most sensitive while lesions are in

the vesicular-pustular stage. Sensitivity rapidly declines as lesions ulcerate and crust. Direct immunofluorescent antibody testing is more rapid (4–6 h) than culture, but does not differentiate between HSV-1 and HSV-2.

Enzyme-linked immunosorbent assay (ELISA) testing for HSV antigens in clinical specimens is a rapid alternative to culture (results in 3–4 h), but its use is generally confined to large laboratories and teaching institutions. Microscopy of Papanicolaou smears or Giemsa staining (Tzanck test) is insensitive and nonspecific and not recommended for the diagnosis of genital herpes. A type-specific antibody test based on HSV glycoprotein G is the most important and reliable diagnostic tool for HSV infection. Antibody tests based on complement fixation, indirect immunofluorescence, or neutralization technologies do not distinguish antibodies to HSV-1 from HSV-2. A negative antibody test result is reassuring in that it excludes the diagnosis in a patient who has symptoms suggestive of recurrent herpes, though testing should be repeated, if negative, in an individual with a history concerning for initial infection as seroconversion may be delayed. A positive test result that is not HSV glycoprotein G based is of little diagnostic value because it does not distinguish reliably between type 1 and type 2 infections and more than one-half of U.S. adults are HSV-1 seropositive. IgM antibody is often present with recurrent HSV outbreaks and does not indicate recent infection. IgM antibodies are only indicated for the evaluation and diagnosis of neonatal herpes infection.

The new type-specific serological assays have specificities of over 98% for the detection of HSV-2 antibody and sensitivities of higher than 90%, depending on the population studied. False positives for HSV-2 can be seen with the most commonly used serologic assay, HerpeSelect, at index values between 1.1 and 3.5. Values in this range, especially in asymptomatic individuals, should have confirmation testing with another test such as Biokit (a point of care test) or the HSV Western blot. The HerpeSelect is relatively insensitive for detection of HSV-1 antibody. Positive serologic tests for HSV-1 may be indicative or oral or anogenital infection while HSV-2 antibodies imply anogenital infection. A rapid, office-based assay that can be run on serum or fingersticks and provide results in less than 10 min is available. It is imperative to specify a glycoprotein G-based test when ordering an HSV serologic test [25, 26].

The following are the current Food and Drug Administration approved, type-specific assays: Western immunoblot, HerpeSelect HSV-1 and HSV-2 ELISA (Focus Diagnostics, Cypress, CA), HerpeSelect HSV-1 and HSV-2 immunoblot (Focus Diagnostics, Cypress, CA), BioKit HSV-2 Rapid Assay (Biokit USA, Lexington, MA), and Captia HSV-1 and HSV-2 (Trinity Biotech, Wicklow, Ireland) [26].

Management and Therapy

Even in HIV-infected individuals, there is stigma attached to genital herpes, and most patients require reassurance and appropriate counseling. This can be given only if one has full access to the facts and myths surrounding this condition.

Pharmacologic and Other Treatment

Antiviral therapy for initial genital herpes prevents new lesion formation and rapidly reduces viral shedding, infectivity, and the risk of autoinfection. However, it has no effect on preventing subsequent recurrences. When taken continuously, it effectively reduces HSV recurrences and subclinical shedding. Episodic treatment shortens the course of recurrences but the difference, although statistically significant, may not be clinically relevant. The current recommended antiviral regimens for genital herpes cause few adverse effects but serum levels can become elevated when renal function is impaired (requiring a reduction in dosage) (Table 6.1). Acyclovir, famciclovir, and valacyclovir are not FDA-approved for use during pregnancy. Consideration of HSV therapy in HIV-infected pregnant females is the same as for HIV-uninfected pregnant females and is centered

Table 6.1 Drug and dose for a specific type of HSV-2 infection in HIV-infected individuals

Therapy			
Type of infection	Acyclovir	Famciclovir	Valacyclovir
Initial[a]	400 mg po tid, for 7–10 days	500 mg po tid for 7–10 days	1 g po bid for 7–10 days
Episodic	400 mg po tid, for 5–10 days	500 mg po bid for 5–10 days	1 g po bid for 5–10 days
Suppressive	400–800 mg po bid to tid	500 mg po bid	500 mg po bid

[a]Less common in HIV-infected individuals and should be treated as episodic treatment but may require longer course of therapy

on reducing the risk of an active outbreak at the time of labor and delivery. Some experts recommend the use of suppressive HSV therapy during the last month of pregnancy for women with symptomatic recurrent herpes to prevent unnecessary cesarean sections by reducing the likelihood of an outbreak near term [14, 26].

Topical lidocaine jelly 2% is a useful adjunct to oral antiviral drugs in managing severe first episodes in women. It should be applied frequently, and especially before voiding, but for no longer than 24–36 h. There is a theoretical risk of sensitization, but this is very rarely seen in practice. Antifungal or antibacterial agents may be needed to treat secondary infections.

There is no evidence that salt baths, topical antiseptics, lysine, vitamins, or other nonmainstream remedies are more effective than placebo in the treatment or prevention of genital herpes.

Optimal Treatments

First Episodes

After diagnosis, assess the need for further immediate tests if there is clinical suspicion of syphilis, chancroid, primary HIV, or other infection. Tests include darkfield examination, serum for non-treponemal antibody test for syphilis (RPR or TRUST), or treponemal specific antibody if using the reverse algorithm in an individual with no previous history of syphilis. Use of an oral antiviral for 7–10 days should be considered. Symptoms usually resolve in 3–4 days. If this is not the case, consider the possibility of secondary infection. Lesions persisting for longer than 14 days should prompt consideration of repeat serologic testing for syphilis and examination for other genital infections at 2–4 weeks. In individuals with advanced HIV, acyclovir-resistant HSV may cause persistent ulceration. If the initial HSV virologic test results were negative, HSV type-specific serology should be obtained at 6 weeks and again at 3 months after presentation [14, 26].

Recurrent Episodes

Virologic specimens should be obtained from active lesions if the diagnosis has not yet been confirmed. Consider obtaining type-specific serology in patients with atypical lesions, negative virologic tests, or lesions that cannot be tested for the presence of HSV [14, 26].

Other important considerations include: episodic treatment with oral antiviral agents; and counseling of patients on treatment options, including continued episodic therapy that may be started at the first signs or symptoms of an outbreak, or suppressive therapy to prevent recurrences.

Persistent Lesions

HSV resistance should be suspected in an individual on HSV antiviral therapy with persistent or recurrent lesions. HSV viral isolates should be obtained for sensitivity testing or presence of thymidine kinase deficient variants. All acyclovir-resistant strains are also resistant to valacyclovir and almost always famciclovir. Treatment options pose a problem due to toxicity of therapy but include the use of foscarnet (40–80 mg/kg IV q 8 h until clinical resolution) or cidofovir (5 mg/kg once weekly). Topical therapy with the immunomodulating drug imiquimod

Table 6.2 Drug and dose for acyclovir-resistant HSV-2 infection

Topical
Imiquimod 5% applied once daily three times per week and washed off after 8 h Cidofovir 1% compounded and apply topically
Intravenous[a]
Foscarnet 40 mg/kg IV every 8 h Cidofovir 5 mg/kg once weekly for 3–4 weeks

bid, twice daily; po, by mouth; q, every; tid, three times daily
[a]Until lesions heal

may avoid the systemic toxicity of parenteral therapy. Topical cidofovir gel 1%, which must be compounded by a pharmacy, can be applied once daily for 5 consecutive days (Table 6.2) [26–30].

Counseling

First and most importantly, accurate information about all aspects of the disease should be provided. New diagnoses of genital herpes can be emotionally trying and may make comprehension and retention of information difficult. Important information to cover at the first visit includes:

- The availability of effective therapy for primary infection
- The availability of effective therapy for recurrences
- Recurrent episodes tend to be milder than the initial episode.
- Transmission of herpes usually occurs from a partner who was not aware of his or her infection or did not believe he or she was infectious when exposure occurred.
- Daily suppressive therapy can reduce the frequency of outbreaks but, in HIV-infected individuals, does not reduce the risk of either HIV or HSV-2 to susceptible partners.
- Condom use >25% of the time can reduce transmission of HSV by 50% and is important to emphasize in light of HIV treatment as prevention and the use of PrEP in HIV-uninfected partners [31]. A recently published study of HIV-1 and HSV-2 serodiscordant couples from East and Southern Africa, found condoms reduced the per-act risk of transmission by 65% from women to men and by 96% from men to women [32].
- Time should be taken at follow-up visits to address the patient's concerns and to provide appropriate counseling. Patients may be given written information and referred to Internet web sites and telephone hotlines (see Additional Resources).

Prevention

The majority of patients, once educated on the mild signs and symptoms of outbreaks, will recognize symptomatic outbreaks. The following steps can help prevent the acquisition and transmission of genital herpes:

- Disclosure of HSV status to sexual partners
- Abstinence during outbreaks
- Condoms can reduce transmission, especially during the first 6–12 months after initial infection. Condoms are more effective in reducing transmission from an HSV-2 infected male to either a male or female noninfected partner than in reducing acquisition to a male from an infected female partner [32].
- Choosing partners with like serologic status
- Daily suppressive therapy: daily suppressive therapy in non-HIV-infected individuals has been shown to reduce the risk of HSV transmission to an uninfected partner

by ~50%. Daily suppressive therapy does not reduce transmission of HSV-2 from HSV-2/HIV-1 confected individuals [26, 33].

Future Directions

Preventive and therapeutic vaccines are currently in Phase 2 and Phase 3 clinical trials. Clinical efficacy data on these vaccines will be available in 2–3 years. Studies in HIV-infected individuals are likely to follow proven clinical efficacy in HIV negative individuals. Even with an effective vaccine, questions concerning the acceptability of a STI vaccine for the general public, and whether the target population should be preteens or young adults, will need to be addressed. Vaginal microbicides may also provide future benefit. In a recent study the application of pericoital tenofovir gel reduced HSV-2 acquisition, with 9 women needing to be treated to prevent 1 additional new infection. The development of vaginal microbicides will offer women protection against HSV and a broad array of other STIs [34, 35].

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Provides important insights on impact of diagnosis on patients and gives clear guidance for counseling.
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Internet Resources

43. American Social Health Association www.ashastd.org ASHA National Herpes Hotline: (919) 361–8488.
44. American College of Obstetricians and Gynecologist www.accog.com.
45. CDC Division of Sexually Transmitted Diseases www.cdc.gov/std.
46. CDC National STD Hotline: English: 800-227-8922, (800) 342-2437 Spanish: (800) 344–7432 www.webMD.com.

Trichomonas vaginalis Infections

7

Christina A. Muzny and Patricia Kissinger

Introduction

Trichomonas vaginalis is the most common curable sexually transmitted infection (STI) worldwide, with prevalence rates eclipsing *Chlamydia trachomatis, Neisseria gonorrhoeae*, and syphilis combined. Since it was first discovered in 1836 by the French physician and microbiologist Alfred R. Donné, understanding of its role in reproductive morbidity and HIV transmission has grown, particularly over the last few decades [1]. HIV providers should be aware of the significance of the pathogen, how common it is, the varied clinical presentations, the caveats of drug therapy, and the nuances of possible treatment failure.

Basic Science Concepts with Regards to *T. vaginalis*

T. vaginalis is a flagellated parasitic protozoan, which takes on three forms: pseudocyst, amoeboid, and trophozoite. The latter form is typically considered the infective form [2]. The trophozoite organism is 10–20 μm long and 2–14 μm wide. Four flagella project from the anterior portion of the cell and one flagellum extends backwards to the middle of the organism, forming an undulating membrane [3]. An axostyle extends from the posterior aspect of the organism. *T. vaginalis* has a large genome (strain G3, 176,441,227 bp) with ~60,000 protein coding genes organized into six chromosomes [4].

T. vaginalis primarily infects the squamous epithelium of the genital tract. It resides in the female lower genital tract and the male urethra and prostate, where it replicates by binary fission. *T. vaginalis* is mostly transmitted among humans by sexual intercourse. Infection may persist for long periods of time, possibly months or even years in women, but generally persists less than 10 days in men due to high rates of spontaneous resolution [5–7]. Incubation time in humans is generally between 4 and 28 days [8]. The *T. vaginalis* pseudocyst form has been found to be more virulent in animals and could have relevance for humans, particularly in the case of cervical neoplasia [9, 10]. The organism can also be infected with double-stranded RNA (dsRNA) viruses which have been shown to dramatically increase the severity of the infection and the likelihood of complications such as pelvic inflammatory disease [11]. Although there is some evidence that protection may be achieved by immunization of laboratory animals [12], protective immunity does not seem to follow natural infection in humans.

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There is some anecdotal evidence of nonsexual transmission of *T. vaginalis* via fomites, and possible water transmission has been described [13–16]. There are several reports of indirect methods of sexual transmission of trichomoniasis among women who have sex with women (WSW), including digital-vaginal transmission [16] and transmission through mutual masturbation [17]. Iatrogenic transmission of *T. vaginalis* by a traditional healer to a patient following genital manipulation has also been reported from The Gambia [18]. Despite these few instances, the data suggest that nonsexual transmission and indirect methods of sexual transmission of *T. vaginalis* are rare [19–21].

T. vaginalis is recognized as a risk factor for the acquisition and transmission of HIV [1, 22–25]. Several cross-sectional and cohort studies have indicated a higher risk for HIV acquisition among *T. vaginalis*-infected compared to *T. vaginalis*-uninfected women [1]. While the exact mechanism whereby *T. vaginalis* amplifies HIV acquisition is not known, there are at least three hypotheses for this increased risk: (1) an inflammatory response to *T. vaginalis* infection results in the increased appearance of HIV target cells in the area [26], (2) *T. vaginalis* infection can impair the epithelial mechanical barrier to HIV [27], and (3) *T. vaginalis* infection may change the normal vaginal flora rendering it more permissive for BV [28], which, in turn, can increase the risk of HIV acquisition [29].

T. vaginalis infection is known to elicit an aggressive local cellular immune response in the vaginal epithelium and exocervix of women, inducing a large infiltrate of CD4+ lymphocytes and macrophages which can bind HIV and facilitate its access [30, 31]. It can also cause punctate mucosal hemorrhages in the lower genital tract, allowing direct access of HIV to the bloodstream through breaks in the mucosal barrier [22]. In addition, *T. vaginalis* has the capacity to degrade secretory leukocyte protease inhibitor [32], known to inhibit entry of HIV into monocytic cells in vitro [33]. Some have hypothesized that *T. vaginalis* can pass viruses, such as HIV, by ingesting the virus and releasing the virus upon cell death or by the endocytic pathway [2].

There has been recent evidence that there is an interaction between *T. vaginalis* and the vaginal microbiota among women. It is hypothesized that *T. vaginalis* may alter the vaginal microbiota in a manner that is favorable to its survival and/or transmissibility [34, 35]. *T. vaginalis* is significantly more common among pregnant women with an intermediate Nugent score (4–6) than in pregnant women with a normal (0–3) or BV-defined (7–10) Nugent score [36]. In addition, Nugent score defined-BV has been found to be a risk factor for the acquisition of *T. vaginalis* [37]. *T. vaginalis* has also been found to occur more often in women with a newly identified species of *Mycoplasma* called Mnola or *Candidatus Mycoplasma girerdii* [35, 38]. Brotman et al. found that *T. vaginalis* was associated with vaginal microbiota consisting of low proportions of lactobacilli and high proportions of *Mycoplasma*, *Parvimonas*, *Sneathia*, and other anaerobes [39].

In a screening study of HIV-infected women, the prevalence of *T. vaginalis* was higher among women who had altered vaginal flora and the majority (61.0%) of HIV-infected/*T. vaginalis*-infected women also had BV [40]. The stat 2 g dose of MTZ for *T. vaginalis* has failed more frequently in HIV-infected women with BV than in HIV-infected women without BV [40]. This high rate of BV that accompanies *T. vaginalis* infection among HIV-infected women has implications for treatment decisions since multi-dose MTZ is recommended for BV. Martin et al. found that *T. vaginalis* prevalence was highest in the women with intermediate Nugent scores confirming the observations of Hillier et al. [36] and Gatski [40]. A heat map analysis of pyrosequencing data showed that the vaginal flora of 18/30 *T. vaginalis*-infected women had a similar unique microbiota characterized by high abundance of *Mycoplasma ssp.* or *Ureaplasma ssp*. and relatively low abundance of *Lactobacillus spp.* and *Gardnerella spp.* [35],

suggesting that *T. vaginalis* directly influences the microbial environment and confirms the potential importance of interactions between *T. vaginalis* and the vaginal microbiota.

Case Illustration

A 55-year-old post-menopausal African American female with HIV on anti-retroviral therapy (CD4 800 cells/mm^3, HIV viral load <20 copies/mL) presents to the HIV clinic for her annual gynecological exam. The patient reports that her primary sexual partner is an HIV negative male that she has been with for the past 5 years. She states that they only use condoms sometimes during sexual intercourse. She also reports having a "fling" a month ago with a new male sexual partner with whom she did not use a condom. For the past 2 weeks, the patient has been having a foul smelling vaginal discharge. She also reports dysuria and increased urinary frequency. A pelvic examination was performed with foul smelling, frothy, thick vaginal discharge noted. There was no cervical discharge or cervical motion tenderness. The vaginal pH was elevated at 6.0. A wet mount of her vaginal secretions showed motile trichomonads (Fig. 7.1). Whiff test was positive. There were no budding yeasts noted upon addition of KOH. Urinalysis was positive only for 1+ leukocyte esterase. The patient was diagnosed with trichomoniasis and treated with metronidazole 500 mg orally twice daily for 7 days per the 2015 Centers for Disease Control and Prevention (CDC) STD Treatment guidelines [41]. She was counseled to abstain from alcohol use while on this medication. In addition, it was recommended that both of her male sexual partners receive treatment as contacts to trichomoniasis. Finally, the patient was counseled to avoid sexual activity until she finished her metronidazole course and all of her sexual partners had been treated. Urine nucleic acid amplification testing for gonorrhea and chlamydia was subsequently negative.

Epidemiology

T. vaginalis is the most common nonviral sexually transmitted infection (STI) in the world. While not a reportable disease, the World Health Organization estimated that there were 276.4 million cases in 2008 and nearly 90% of these infections occurred among people living in resource-limited settings [42]. *T. vaginalis* is more prevalent that *Chlamydia trachomatis, Neisseria gonorrhoeae*, and syphilis combined. The global prevalence of *T. vaginalis* has been estimated at 8.1% for women and 1.0% for men [43]. These rates are likely underestimated as they are derived from studies that used microscopy rather than the more sensitive nucleic acid amplification tests (NAAT) [44, 45]. The large difference in rates by sex may be related the availability of iron during the menstrual cycle, a major metabolic requirement for *T. vaginalis* growth [46], higher rates of spontaneous resolution in men, (5–7) or greater difficulty in detecting the parasite in men [47].

Because there are no surveillance programs in place, the epidemiology of *T. vaginalis* is not completely known. It is known, however, to vary greatly by population and geography. In the United States, two population-based studies that used PCR testing found rates of 2.3% among adolescents [48] and 3.1% among women ages 14–49 [49]. Population-based studies in Africa show distinctly higher rates. In Zimbabwe, the rate was 9.5% among both genders using antibody testing [50]. Using NAAT, the positivity rate among men in Tanzania was 11% [51]. Women in Papau New Guinea also appear to have exceptionally high *T. vaginalis* rates ranging from 21% in pregnant women to 42.6% in the general population [52, 53]. Other population-based studies that used NAAT testing among reproductive-age women in other parts of the world found lower rates of infection (i.e., <1% in rural Vietnam [54], Flanders, Belgium [55], and Shandong Province in China [56]). Screening rates among women attending antenatal or family-planning clinics are often used as an indicator of the prevalence in the

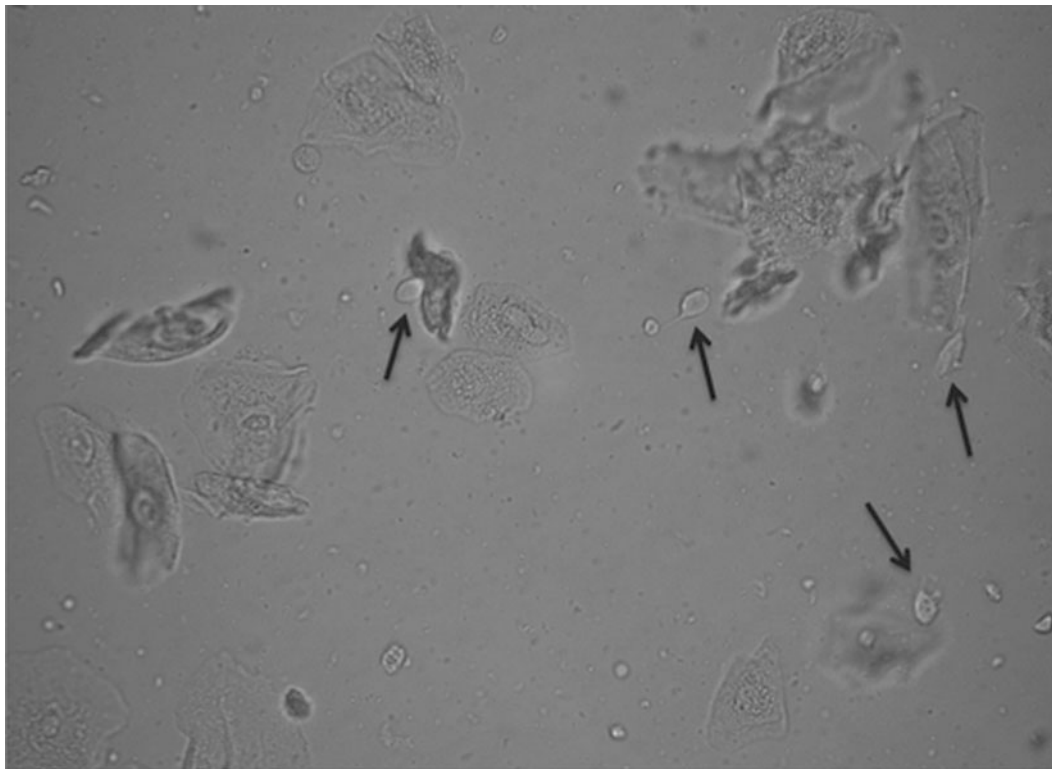

Fig. 7.1 *Trichomonas vaginalis* on wet prep microscopy. Saline wet mount demonstrating *Trichomonas vaginalis* among squamous epithelial cells. *Arrows* indicate *T. vaginalis*. Reprinted from [138]

general population. Studies at these sites found prevalence rates from 3.2% to 52.0% in resource-limited settings and 7.6 to 12.6% in the US [57]. Thus, rates of *T. vaginalis* vary greatly and are dependent on the characteristics of the population studied.

In general, Africans or persons of African descent have higher rates of *T. vaginalis*, as evidenced by higher rates in Sub-Saharan Africa [50, 51], high rates among persons of African descent such as Garifunas [58], and high rates among African Americans in the US [49, 59]. In the US, the highest prevalence of *T. vaginalis* infection in women is seen among African Americans with rates ranging from 13 to 51% [60]. African American women have rates that are ten times higher than white women, constituting a remarkable health disparity [49]. Other risk factors for *T. vaginalis* include increasing age, incarceration, intravenous drug use, commercial sex work [61] and the presence of bacterial vaginosis (BV) [37].

Studies have shown an association between *T. vaginalis* and vaginitis (BV and vaginal candidiasis), cervicitis, urethritis, herpes simplex virus type-1 and type-2, chlamydia, gonorrhea, and syphilis [62]. *T. vaginalis* has also been associated with poor birth outcomes such as low birth weight, preterm delivery, pelvic inflammatory disease, and premature rupture of membranes [63]. One study showed an association between maternal *T. vaginalis* infection and intellectual disability in children [64]. Although rare, *T. vaginalis* infection can be transmitted perinatally [65] and can cause vaginal and respiratory infections in neonates [66, 67].

In addition to poor reproductive outcomes, *T. vaginalis* has been found to be associated with HIV transmission and acquisition [1]. Mathematic modelers have found that between 6 and

20% of HIV infections among US women could be attributed to *T. vaginalis* [23, 68, 69]. Control of *T. vaginalis*, therefore, may provide a cost-effective strategy for reducing HIV transmission especially in settings where *T. vaginalis* is common [70, 71] or among subgroups who are at higher risk for *T. vaginalis* such as African Americans [22]. Cost-effectiveness studies of *T. vaginalis* screening among HIV-infected women have found it to be cost saving in terms of HIV infections averted in sexual partners [72]. HIV providers should consider *T. vaginalis* screening for both clinical care and for public health.

Prompt treatment of HIV-infected women with *T. vaginalis* is also important. Three studies found increased HIV shedding among women with *T. vaginalis* which was diminished after successful treatment of the organism [73–75]. Increased HIV genital shedding has also been found among HIV-infected men with symptomatic *T. vaginalis* [76]. These data underscore the importance of screening and treatment among HIV-infected persons.

T. vaginalis is associated with other STIs. It appears to have a similar bi-directional association with herpes simplex virus-type II (HSV-2) as it does with HIV. Concomitant infection with *T. vaginalis* has been associated with HSV-2 shedding [77] and women with *T. vaginalis* have a higher incidence of HSV-2 [78]. Evidence also exists that *T. vaginalis* is associated with HPV acquisition and cervical neoplasia. A meta-analysis found that *T. vaginalis* was associated with a 1.9 fold increased risk of cervical neoplasia [79]. Data for the association between *T. vaginalis* and prostate cancer remain controversial [80, 81].

Clinical Presentation

The majority of women (85%) [49] and men (77%) [82] with *T. vaginalis* are asymptomatic. One-third of asymptomatic women become symptomatic within 6 months [8]. Untreated, *T. vaginalis* may be resolved by host immunity [83] but may also remain sub-clinical [84, 85]. Among women, common sites of infection include the vagina, urethra, and ectocervix. Symptoms include vaginal discharge (Fig. 7.2) (which is often frothy, malodorous, and yellow-green), dysuria, itching, and vulvar irritation. The normal vaginal pH is usually acidic with a pH between 3.8 and 4.5, but with *T. vaginalis* infection, the pH becomes more alkaline (although it can, at times, remain normal) [8]. *Coplitis macularis* or strawberry cervix (representing punctuate mucosal hemorrhages in the cervical tissue) (Fig. 7.3) is seen in about 5% of women, though with colposcopy this rises to nearly 50% [86]. Other complications include infection of the adnexa, endometrium, and Skene and Bartholin glands. In men, *T. vaginalis* can cause dysuria, and rarely epididymitis and prostatitis. In addition, it can cause decreased sperm cell motility [87].

Diagnostic Considerations and Recommendations

The diagnosis of *T. vaginalis* is becoming more precise and more tests have become available in the last decade. Table 7.1 summarizes the name of the test, type of test, sensitivity/specificity, and pros/cons of the available test.

Wet mount microscopy has been used for many decades to diagnose *T. vaginalis*, however, it is insensitive, particularly in men. Sensitivities range from 50 to 70% in women depending on the expertise of the reader and should be read within 10 min of collection, which is often logistically challenging. While culture has better sensitivity than wet mount in women, it is more expensive, time consuming, requires incubation, and demonstrates poor sensitivity in men. Culture may also be less sensitive soon after treatment. One study of HIV-uninfected and one study of HIV-infected women found that that after single dose MTZ treatment, *T. vaginalis* infection was nondetectable for months via culture and then reappeared in the absence of reported sexual exposure [84, 90] underscoring the need for more sensitive testing for detecting unresolved infections.

Nucleic acid amplification tests are the most sensitive tests, are moderately priced, but require

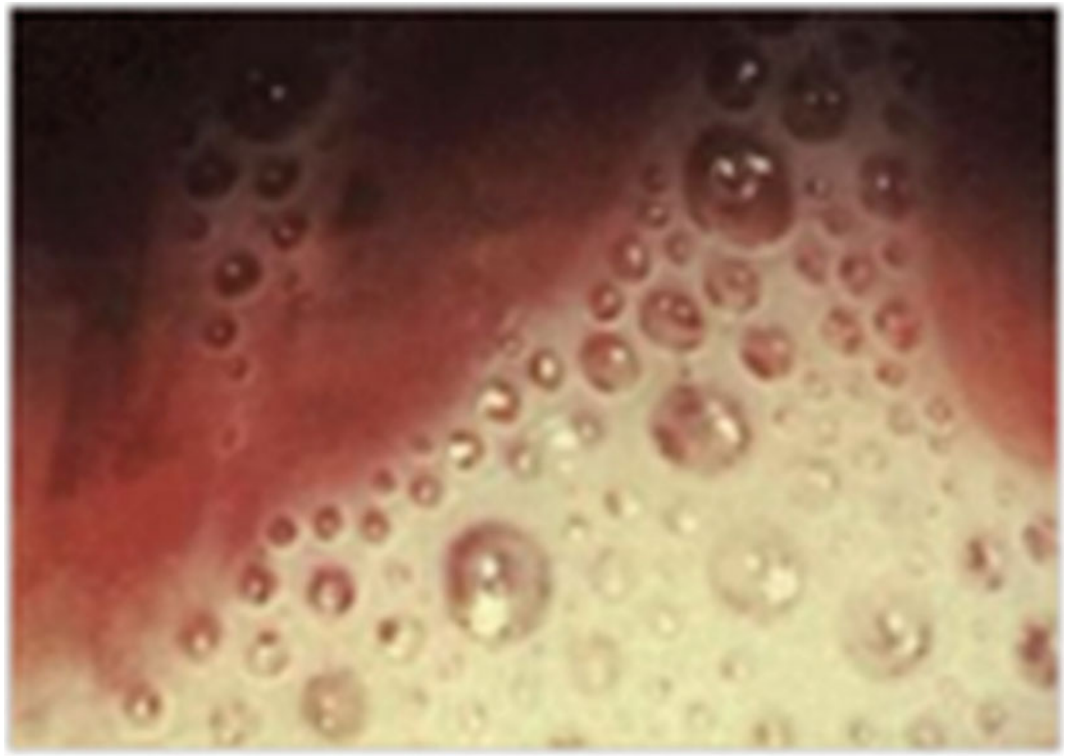

Fig. 7.2 Frothy discharge characteristic of *T. vaginalis.* Reprinted from [88]

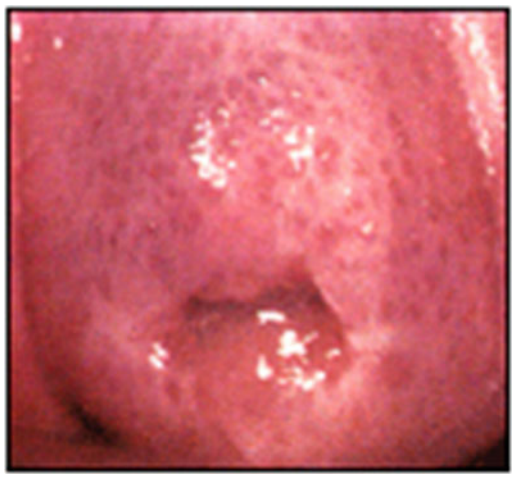

Fig. 7.3 *Coplitis macularis*, or strawberry cervix, seen in some women with *T. vaginalis*. Reprinted from [88]

processing either in-house or at a send out laboratory and therefore are not considered to be point-of-care tests. The APTIMA® *Trichomonas vaginalis* Assay (Hologic Gen-Probe, San Diego, CA) was US Federal Drug Adminstration (FDA)-cleared in 2011 for use with urine, endocervical and vaginal swabs, and endocervical specimens collected in the Hologic® PreserveCyt solution (ThinPrep) from females only. Sensitivity is 95 to 100% and specificity is also 95 to 100% [91]. In resource constrained areas, NAAT usage may be limited by feasibility and cost considerations.

The *T. vaginalis* NAAT has been validated in asymptomatic and symptomatic women in multiple specimen types [92, 93] and is run on the same instrumentation platforms for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* NAAT testing [92, 94]. Although the *T. vaginalis* NAAT can be used to test male urethral and urine specimens, the US FDA has not sought clearance for this purpose [94]. A recent study of 3821 women presenting to a county health department STD clinic found that the *T. vaginalis* NAAT detected approximately one-third more infections among women than wet mount alone [95].

Table 7.1 Common diagnostic tests for *T. vaginalis* [47, 89]

Test name	Type of test	Sensitivity/specificity[a]	Pro/con
Wet prep	Point of care; Microscopy	Sensitivity: 50–70% Specificity: 100%	Pros: The test is inexpensive, relatively easy to perform, and is point of care Cons: Needs to be read within 10 min of collection. Particularly insensitive in men
InPouch™ TV	Culture	Sensitivity: 44–77% Specificity: 100%	Pros: Highly specific Cons: More expensive, time consuming than wet prep, need an incubator to store the pouches, and demonstrates poor sensitivity in men
Hologic Aptima® Trichomonas vaginalis (ATV) assay; Becton Dickenson ProbeTec™ *T. vaginalis* Q^x (TVQ) amplified assay; Cepheid Xpert® TV	NAAT	Sensitivity: 88–100% Specificity: 98–100%	Pros: Highly sensitive, no incubation or refrigeration are needed, can be run on same platform for *C. trachomatis* and *N. gonorrhoeae* NAAT testing Cons: Not point of care, cost higher than non NAAT
Becton Dickenson (BD) Affirm™ VP III	Point of care	Sensitivity: 64% Specificity: 100%	Pros: Point of care, results available within 45 min Cons: Should not be used in asymptomatic women
OSOM® Rapid Antigen Detection Test	Point of care	Sensitivity: 77–98% Specificity: 99–100%	Pros: Point of care, minimal training, results available in 10 min Cons: Should not be used in asymptomatic women

[a]Sensitivities and specificities are reported for women only and are generally lower in men

There are two additional point-of-care tests that have been approved by the US FDA for diagnosis of *T vaginalis* among women: the OSOM® Trichomonas Rapid Antigen Detection Test (Sekisui Diagnostics, Lexington, MA), an immunochromatographic capillary flow dipstick technology [96] and the Affirm™ VP III (Becton, Dickinson & Co., Sparks, MD), a nucleic acid probe test that evaluates for *T. vaginalis*, *G. vaginalis*, and *C. albicans* [97]. Both tests are performed on vaginal secretions and have a sensitivity of more than 83% and a specificity of more than 97%. Results of the OSOM® test are available in about 10 min, while results of the Affirm™ VP III test can be available within 45 min. The Xpert® *T. vaginalis* by Cepheid (Sunnyvale, CA) has been approved by the Federal Drug Administration (FDA) for women and may hold promise in resource poor countries and for point-of-care diagnostics in men, but is not yet FDA approved for use in men [47].

It has been generally thought that only vaginal specimens should be collected for *T. vaginalis* testing among women. There is, however, some evidence that endocervical specimens are suitable. Endocervical specimens have been found to be 88% sensitive and 99% specific for *T. vaginalis* by PCR compared to 90% and 99% for vaginal swab [98]. Huppert showed that endocervical specimens were 100% sensitive and 98% specific by transcription-mediated amplification (TMA) compared to 100% sensitivity and specificity for vaginal specimens using latent class analysis [99].

Because rates of repeat *T. vaginalis* infection are high, the CDC recommends that all women identified with infection undergo rescreening around three months posttreatment, regardless of whether or not they believe that their partner was treated. NAAT testing too soon after treatment can result in detection of remnant trichomonas DNA, thus producing false positives. By 2–3 weeks post treatment most remnant DNA has cleared [100]; however, one study found a 15% false positive rate at 3 weeks [101]. Thus, if testing is done before 3 weeks post treatment,

culture or microscopy may be more appropriate than NAAT.

Treatment

Current Recommendations

For nearly four decades, metronidazole (MTZ) has been the treatment of choice for *T. vaginalis* [102]. MTZ belongs to the 5-nitroimidazole drug family and is reported to have about a 95% success rate in curing *T. vaginalis* along with its related compounds such as tinidazole (TNZ) and seconidazole [103]. While TNZ has higher clearance rates and fewer side effects than MTZ, it is significantly more expensive, thus MTZ is considered the first line of treatment [94]. The World Health Organization (WHO) and the US CDC guidelines for treatment of *T. vaginalis* are described in Table 7.2. Abstinence from alcohol use should continue for 24 h after completion of MTZ treatment or 72 h after completion of TNZ treatment. If a patient fails first line therapy, alternative therapies include more drugs for longer periods of time.

Rates of repeat infections range from 5 to 31% [105–109] and are particularly common among HIV-infected women with rates as high as 37% in this population [110]. Repeat infections are common and share similar sequelae to initial infections. While it is clear that *T. vaginalis* repeat infection rates are unacceptably high, the source of these repeat infections is less clear. Possible sources of retest positives after treatment are: reinfection from an untreated/infected baseline partner, infection from a new partner, and/or treatment failure. Each of these sources of retest positives require a different approach to prevent ongoing infection (Fig. 7.4) [111]. For example, if the cause is re-infection, then assuring that the original partners are treated (see below regarding expedited partner treatment or EPT) is needed. If the source is a new partner or treatment failure, then rescreening is needed. If there is concern for treatment failure, medication resistance testing should be performed.

Consultation and *T. vaginalis* susceptibility testing is available in the US from CDC (telephone: 404-718-4141; website: http://www.cdc.gov/std).

Reported rates of MTZ resistance among mostly non-HIV-infected women range from 2.2 to 9.6% [106, 112–114] and infections were

Table 7.2 Treatment recommendations: CDC versus WHO

	CDC guidelines [41]	WHO guidelines [104]
First line HIV infected	MTZ 500 mg orally twice daily for 7 days	MTZ 2 g orally in a single dose OR TNZ 2 g orally in a single dose (There are no specific recommendations for HIV infected persons)
First line HIV uninfected	MTZ 2 g orally in a single dose OR TNZ 2 g orally in a single dose	MTZ 2 g orally in single dose OR TNZ 2 g orally in a single dose
Alternative HIV uninfected	MTZ 500 mg orally twice daily for 7 days.	MTZ 400 or 500 mg twice daily for 7 days OR TNZ 500 mg twice daily for 5 days
Refractory infections	MTZ 500 mg orally, twice daily for 7 days (if failed MTZ 2 g orally in a single dose) OR (if failed MTZ 500 mg twice daily orally for 7 day course) MTZ 2 g orally for 7 days OR TNZ 2 g orally for 7 days	MTZ 2 g orally, daily, together with 500 mg applied intravaginally each night for 3–7 days OR MTZ 400 mg or 500 mg orally, twice daily for 7 days

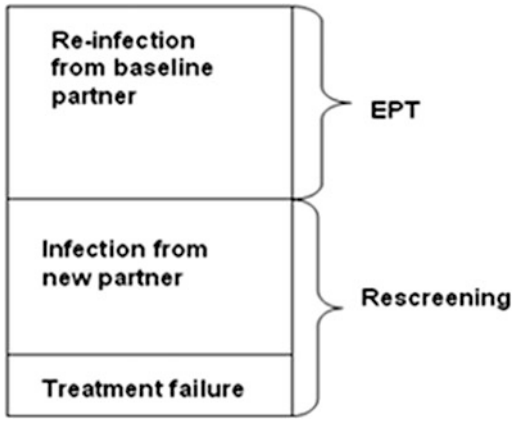

Fig. 7.4 Possible causes of a repeat TV+ test after treatment among TV-infected persons

usually resolved with repeat MTZ treatment at the same or higher dosage [114]. In one study of HIV-infected and HIV-uninfected women, a large proportion of the repeat infections were attributed to treatment failure (i.e., no sexual exposure and no drug resistance) [105]. Repeat *T. vaginalis* infections among HIV-infected women are substantially higher than in HIV-uninfected women with rates between 18.3 and 36.9% [105, 110, 115] and immune status (i.e., CD4 count) was not associated with repeat infections. The molecular mechanism(s) of clinical resistance are poorly understood.

Sexual partners of patients with *T. vaginalis* should be treated. Commonly, patients are told by their providers to tell their partners to seek testing and treatment. This can be problematic because sensitive tests for men are not readily available. Providers may consider treating partners of positive patients presumptively. One method of presumptive partner treatment is expedited partner therapy (EPT). EPT is the clinical practice of treating the sexual partners of patients diagnosed with an STI by providing prescriptions or medications to the patient to take to his/her partner without the health care provider first examining the partner.

One RCT demonstrated that partner treatment with 2 g TNZ resulted in a > fourfold reduction in repeat infections among *T. vaginalis*-infected index women [116]. Two other studies using 2 g MTZ for male partners of *T. vaginalis*-infected women found no effect of EPT [107] or a borderline effect [117]. While it is possible that the two studies that used MTZ were either underpowered or did not use the correct control arm, it is also possible that TNZ is a better treatment for men.

The most common reactions reported from metronidazole are metallic taste in the mouth in addition to nausea and vomiting. Less commonly, urticaria, facial edema, flushing, fever, and anaphylactic shock from an immediate-type hypersensitivity reaction have been reported. Desensitization, in consultation with an allergist, can be done for this type of severe allergic reaction, but only has about a 42% success rate [118].

If *T. vaginalis* remains persistent or the patient is allergic to 5-nitroimidazole medications, other intravaginal treatments have been used anecdotally or are under investigation including: Acetarsol [119], boric acid [120, 121], furazolidone [121], and paromomycin [122]. Nitazoxanide was also examined as an alternative oral agent for MTZ-resistant *T. vaginalis* but was not found to be very effective [123]. Combination therapy including TNZ plus ampicillin (doxycycline for penicillin-allergic patients) plus clotrimazole pessaries for 7 to 14 days has demonstrated success in 9/11 (81.8%) patients in one small series [124]. Some plant extracts have shown anti- *T. vaginalis* activity, but these have not yet been tested in clinical trials [125].

In a randomized clinical trial (RCT) among HIV-infected women with *T. vaginalis*, multi-dose MTZ was found to be superior to single dose treatment [126]. Further analysis revealed that the superiority is only in the presence of BV [40]. Since there is a high co-occurrence of *T. vaginalis* and BV [127–130], recommendations are to treat HIV-infected women with the multi-day dose of MTZ [41]. A recent meta-analysis of 6 studies with mostly HIV-uninfected women, also found superiority of multi-dose MTZ to single dose [131].

Studies have also found that both nevirapine- and nonnevirapine containing anti-retroviral therapy (ART) may interfere with the efficacy of MTZ among HIV-infected women [132, 133]. The mechanisms whereby ART interfere with MTZ treatment of *T. vaginalis* are not well understood but may be due to metabolic interference between the two drugs.

MTZ is a class B drug and several meta-analyses have found it to be safe in pregnant women in all stages of pregnancy [134, 135]. TNZ has not been evaluated in pregnant women and remains a class C drug. Treatment with 2 g MTZ is recommended by CDC at any time during pregnancy [136], whereas WHO does not recommend treatment in the first trimester unless it is indicated for prevention of untoward birth outcomes. Both entities suggest the 2 g dose during pregnancy, but no studies have compared 2 g to multi-dose MTZ among pregnant HIV-infected women.

In lactating women who are administered MTZ, withholding breastfeeding during treatment and for 12–24 h after the last dose will reduce the exposure of the infant to metronidazole. For women treated with TNZ, interruption of breastfeeding is recommended during treatment and for 3 days after the last dose [137].

Emerging Strategies

Table 7.3 describes alternative treatments in the case of nitroimidazole drug resistance or drug allergy. It should be noted that the effectiveness of these treatments has only been determined anecdotally.

Providers should consider consultation with an allergist for possible desensitization for women with severe metronidazole hypersensitivity reaction.

Prevention

Prevention of *T. vaginalis*, as with all STIs, is to use protective barrier methods (i.e., latex condoms, condoms on sex toys, etc.) and reduce the number of sexual partners. Male circumcision may also protect men against *T. vaginalis* [143].

Table 7.3 Alternative Treatment Options for *T. vaginalis* in the Setting of Nitroimidazole Drug Resistance or Severe Allergy[a]

Agent and Regimen	Cure Rates
Intravaginal boric acid (applied in a gelatin capsule containing 600 mg boric acid) twice daily X 2 months [120]	1/1 cured (100%)
Intravaginal paromomycin cream (5 g of a 5% cream administered nightly) and high dose oral tinidazole (1 g orally tid) X 14 days [122]	2/2 cured (100%)
Intravaginal furazolidone (100 mg per 5-g applicator of 3% nonoxynol-9) twice daily X 12 days [121]	1/1 cured (100%)
Intravaginal boric acid (applied in a gelatin capsule containing 600 mg boric acid) alternating nightly with intravaginal clotrimazole cream X 1-5 months [139]	2/2 cured (100%)
Intravaginal 6.25% paromomycin cream (250 mg per 4-g applicator, one applicator used nightly) X 2-3 weeks [140]	6/9 cured (66.6%)
Intravaginal povidone-iodine (Betadine) douches, 20 cc of a 10% solution twice daily for 2 days per week X 2 weeks (leave in the vagina for 10 min) [141]	1/1 cured (100%)
Nonoxynol-9 100 mg intravaginal suppository [142]	1/1 cured (100%)

[a] Reprinted with permission from [138]

Conclusion

T. vaginalis is a highly prevalent and treatable STI with important reproductive health morbidity and has been associated with increased acquisition and transmission of HIV. *T. vaginalis* may increase HIV susceptibility by increasing inflammation, impairing the epithelial barrier and/or by changing the vaginal flora, making HIV infection more likely. *T. vaginalis* is common among HIV-infected women with rates over three times higher than HIV-uninfected women. The recommended 2 g MTZ treatment is not as effective with HIV-infected women and multi-dose treatment is recommended by CDC. Co-infections with BV and ART usage may interfere with the effectiveness of MTZ for *T. vaginalis* treatment. While not recommended for the general population, screening for *T. vaginalis* infection among HIV-infected women is recommended by CDC and may be cost saving because of the potential to avert new HIV infections.

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8 Prevention of Complications from Human Papillomavirus Infection in the HIV-Infected Individual

Cristina Elena Brickman and Joel Palefsky

Introduction

The advent of antiretroviral therapy (ART) has led to a marked increase in the life expectancy of people living with HIV (PLWH) [1] and a growing interest in the long-term complications of HIV infection.

The effects of human papillomavirus (HPV) infection are of particular interest. Human papillomaviruses are a family of small non-enveloped DNA viruses that infect epithelial cells [2]. Approximately, 40 HPV types specifically infect the anogenital and upper digestive tract and are sexually transmitted [2]. The lifetime risk of anogenital HPV infection is 75–80% among all sexually active men and women [3], rendering HPV the most common sexually transmitted agent [4].

Of the anogenital HPV types, fifteen to twenty are considered oncogenic or "high-risk" (hr-HPV) [5]. Infection with hr-HPV leads to development of squamous intraepithelial lesions (SIL), and persistent hr-HPV infection may, in some cases, lead to the cancer precursor high-grade SIL (HSIL). A small proportion of HSIL in turn progresses to invasive squamous cell carcinoma (SCC) giving rise to 99.9% of cervical cancers, 90% of anal cancers, and the majority of oropharyngeal, vaginal, penile, and vulvar cancers [6].

The hr-HPV type 16 carries the strongest association with invasive cancer: it is detected in over 50% of cervical cancers, 85% of anal cancers, and almost 90% of HPV-positive oropharyngeal cancers [7]. HPV type 18 is the second most common type associated with cervical cancer (detected in approximately 20% of specimens), but is less prevalent at other cancer sites [7].

While infection with hr-HPV can lead to LSIL or HSIL, infection with low-risk HPV types (lr-HPV) is associated primarily with low-grade squamous intraepithelial lesions (LSIL), which include genital warts or condylomata. Lr-HPV types 6 and 11 cause 90% of genital warts [8]; these are of low oncogenic potential but can be difficult to eradicate and often lead to discomfort and psychological distress.

Infection with anogenital HPV is particularly common in PLWH compared with the general population. PLWH are also more susceptible to developing HSIL and progression to invasive cancer [9]. This, coupled with the longevity of PLWH on ART and the potential to prevent HPV-associated cancers, highlights the need for suitable prevention programs in this population.

In this chapter, we discuss the mechanisms that facilitate HPV infection and the most current epidemiology of the two most common

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HPV-associated malignancies: cervical and anal cancer. We also discuss potential strategies for early detection and/or prevention of HPV-related cancers in PLWH.

Pathogenesis of HPV Infection

Initial Infection

Anogenital HPV types preferentially infect areas of metaplasia in both the cervix and the anus [5, 10]. These areas, referred to as transformation zones, are sites where columnar glandular epithelium is actively being replaced by stratified squamous epithelium. To establish infection, the virus first accesses the basal cells of the epithelium, a process that occurs at sites of microtrauma [11]. Changes in receptors, adhesion molecules, and inflammatory mediators associated with metaplasia are thought to facilitate access of HPV to the basal cell layer [12].

The HPV genome is composed of double-stranded circular DNA that is approximately 8 kb long. The genome can be divided into an *early* region, which codes for the E1, E2, E4, E5, E6, and E7 proteins, and a *late* region, which codes for two structural capsid proteins termed L1 and L2 [13]. Between these two regions lies the upstream regulatory region (URR) or long control region (LCR). The URR is a noncoding portion of the genome that contains four binding sites for E2 as well as for multiple transcription factors (Fig. 8.1).

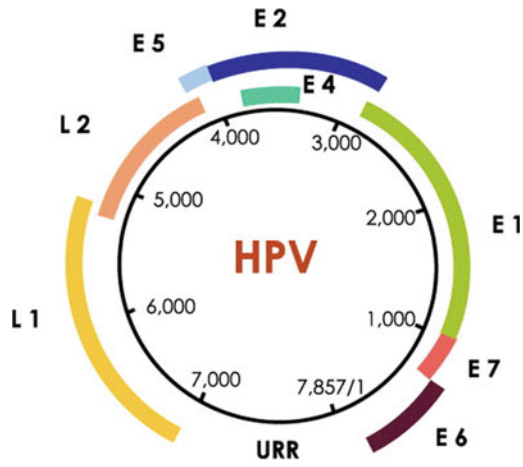

Fig. 8.1 Schematic presentation of the HPV genome showing the arrangement of the early E or nonstructural genes, the late L capsid structural genes (L1 and L2) and the URR. Reprinted from [140]

Once in the basal layer, the viral genome is maintained as a relatively quiescent episome. Protein expression and active HPV replication increase as infected cells migrate into the suprabasal cell layers and undergo epithelial differentiation, a process that may result in changes that are clinically and histopathologically recognized as SIL. However, latently infected cells likely also persist within the basal cell epithelium [14, 15] with the potential to reactivate at some point in the future and lead to SIL.

Classification of Squamous Intraepithelial Lesions

The Bethesda System was developed in 1988 to classify the cytologic changes that result from HPV infection [16]. This nomenclature reflected a morphologic continuum in which lesions progressed from low-grade dysplasia to progressively higher grade disease, and eventually, invasive cancer. Low-grade lesions were termed LSIL on cytology, and cervical intraepithelial neoplasia grade 1 on histology. High-grade lesions were designated high-grade squamous intraepithelial lesions (HSIL) on cytology and cervical intraepithelial neoplasia (IN) grades 2 and 3 on histology. However, it is now known that the majority of low-grade lesions are transient and do not progress to high-grade dysplasia, even with hr-HPV infection [5, 17], and HPV infection is increasingly thought to progress via two distinct pathways resulting in either low-grade (benign) or high-grade (precancerous) lesions.

The Lower Anogenital Squamous Terminology (LAST) Project of the College of American Pathologists and of the American Society for Colposcopy and Cervical Pathology now

recommends using p16 immunohistochemistry, a biomarker for cellular proliferation, to clarify the diagnosis of IN 2 by classifying all p16-negative IN 2 lesions as "LSIL" and all p16-positive IN2 and all IN3 lesions as "HSIL" [18].

In this paradigm, LSIL reflects active HPV replication and virion formation while HSIL reflects HPV-induced transformation (Fig. 8.2) [19]. This classification has therapeutic implications: LSIL is not considered precancerous and does not need to be treated, whereas HSIL is sought and treated to reduce the risk of progression to cancer. The LAST project also recommended extending LSIL/HSIL terminology to histopathologic grading of disease in addition to cytology grading and using uniform terminology across all anogenital sites where HPV infection occurs.

Development of HSIL

Persistent HPV infection and development of HSIL involves two key HPV oncogenes: E7 and E6 [11]. E7 binds to the proto-oncogene *retinoblastoma* (Rb), which results in release of the host E2F transcription factor from Rb and cellular entry into the cell cycle S-phase. E2F release also leads to up-regulation of the tumor-suppressor protein p16. P16 works to inhibit Rb inactivation and hence stop replication. While its effect is insufficient to counteract E7-driven cellular proliferation, p16 staining is a widely accepted marker of E6/E7 cellular proliferation that can be used to distinguish between LSIL and HSIL [18].

E6 binds and inactivates the tumor suppressor protein p53, which induces DNA repair enzymes

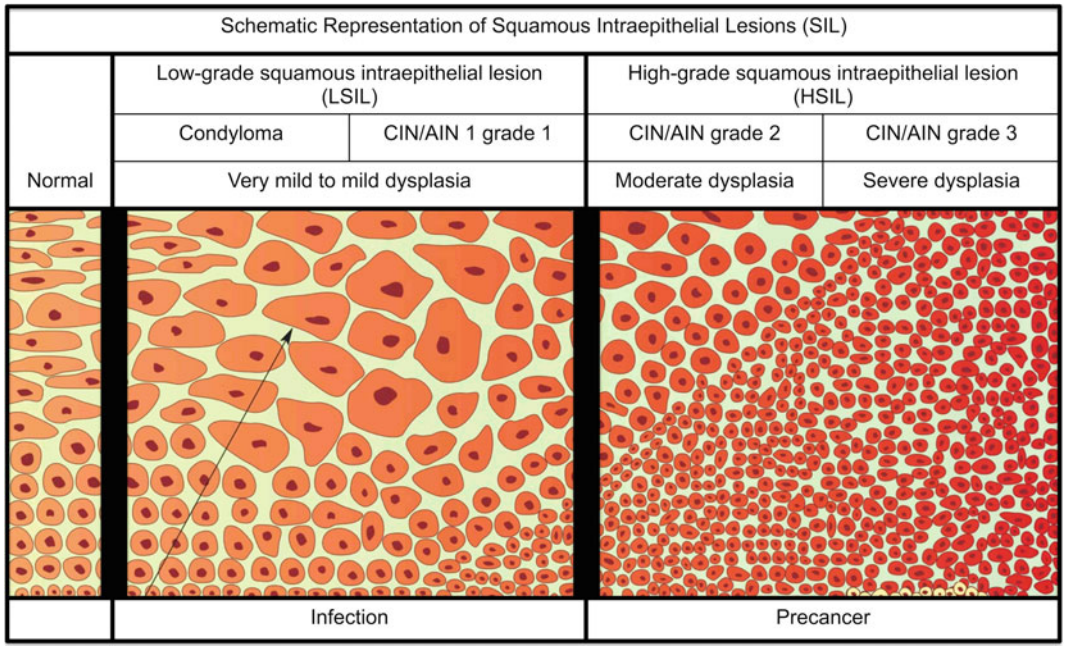

Fig. 8.2 Schematic representation of the two-tiered system to classify cytology and histology of squamous intraepithelial lesions. Cervical intraepithelial neoplasia (CIN) grade 1, anal intraepithelial neoplasia (AIN) grade 1 and condylomas are termed LSIL. CIN/AIN grades 2 and 3 are termed high-grade squamous intraepithelial lesions (HSIL). The new classification reflects the distinct biology underlying LSIL and HSIL. Adapted from [141]

and cellular apoptosis when DNA damage cannot be repaired. Thus, E7 increases the rate of mutations by enhancing replication and E6 allows these mutations to accumulate (Fig. 8.3). This results in progressive genomic instability that can eventually lead to invasive cancer. The E5 protein also contributes to malignant transformation by reducing turnover of epidermal growth factor receptors on the cell surface, thus rendering cells more susceptible to the mitogenic effects of epidermal growth factor.

Integration of HPV DNA into the cellular genome is another transformative mechanism. The E2 gene codes for a trans-activating protein that binds the LCR of the HPV genome and down-regulates E6 and E7 expression (see Fig. 8.3). HPV integration disrupts the E2 gene and the loss of E2 binding to the LCR in turn increases E6 and E7 expression [20].

The mechanisms determining whether HPV is transforming, resulting in HSIL and cancer, or primarily replicative, leading to LSIL, are not fully understood. One major determinant is HPV type; differences in function and cellular affinity of the E6 and E7 proteins of hr-HPV types compared with lr-HPV types predispose infected cells toward the transformative pathway [21]. As mentioned, HPV-16 in particular is much likelier to result in persistent HPV infection, HSIL and cancer than infection with lr-HPV types and other "intermediate risk" hr-HPV types [5]. The processes regulating integration are also unknown although epigenetic changes such as DNA hypermethylation, histone deacetylation, and differential expression of micro-RNAs may play a role [20, 22].

Interactions Between HIV and HPV

Based on the limited effect of immune-reconstitution with ART on HSIL and anogenital cancer incidence (see "Effect of Immune-reconstitution with ART"), HIV is thought to facilitate initial infection and development of precancerous lesions but to play less of

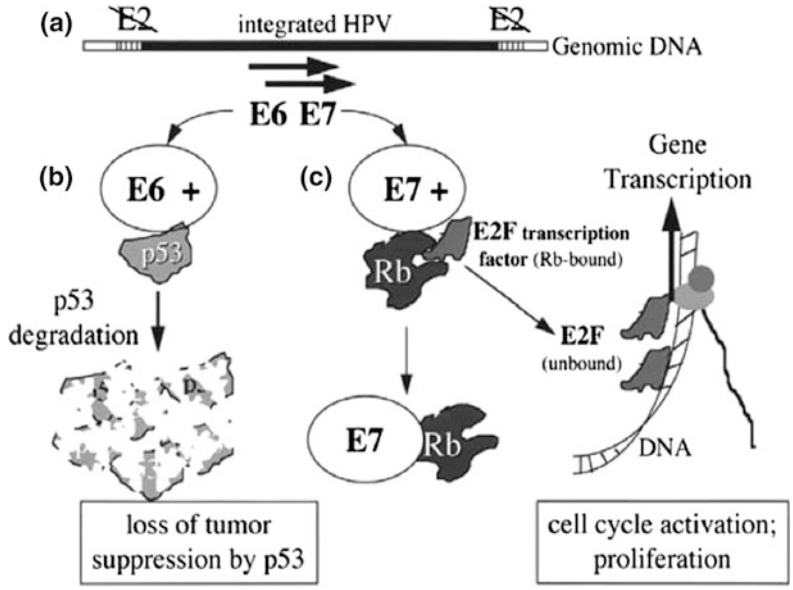

Fig. 8.3 **a** HPV DNA integration disrupts the E2 gene resulting in up-regulation of E6 and E7 expression. **b** E6 binds and inactivates the tumor suppressor protein p53 resulting in loss of DNA repair and cellular apoptosis when DNA damage cannot be repaired. **c** E7 binds to the proto-oncogene *retinoblastoma* (Rb), resulting in release of the host E2F transcription factor from Rb and cellular entry into the cell cycle S-phase. Reprinted from [142]

a role in malignant transformation once HSIL is present [9]. Enhanced HPV infection and HSIL development occurs through several different mechanisms including disruption of epithelial cell tight junctions [23], interference with viral clearance and reactivation of latent HPV. Both HIV-1 tat (transactivator protein), which may be secreted by HIV-infected immune cells, and HIV gp120, which can be found in the tissue microenvironment of PLWH, disrupt epithelial tight junctions [23]. Treatment of mucosal epithelial tissue explants with tat and gp120 increases the passage of HPV-16 pseudovirions to the basal cell layer, where initial HPV infection occurs. Tat also up-regulates E6 and E7 expression in HPV 16-positive human oral keratinocytes in vitro, suggesting an additional role in facilitating HSIL once infection is established [24].

Cell-mediated immunity is necessary for the resolution of HPV infection, as highlighted by the infiltration of CD4+ T cells, CD8+ T cells, and macrophages that occurs immediately prior to spontaneous LSIL resolution [25]. The rapid and irreversible loss of CD4+ T cells from mucosal lymphoid tissue that occurs soon after HIV infection [26] is hypothesized to hinder SIL resolution. Furthermore, disruption of mucosal immunity may also facilitate reactivation of HPV latent within the basal cell layer of epithelium. This theory is supported by the substantial proportion of new cervical HPV infections detected in nonsexually active HIV-infected women [27], and by the markedly increased rates of cervical HPV infection that occur immediately following HIV infection compared with HIV-uninfected women [28, 29].

Case Illustration

A 38-year-old man with a history of HIV presented to the University of California San Francisco Anal Neoplasia Clinic for Research and Education (ANCRE) with 6 months of worsening anal pain. HIV was diagnosed at age 24 with risk factors including intravenous methamphetamine use and unprotected sex with multiple male partners. His HIV infection had been poorly controlled due to medication non-adherence with a CD4 nadir of four cells per microliter 5 years earlier.

The patient was first seen at ANCRE 4 years earlier with complaint of perianal condylomata. High-resolution anoscopy (HRA) was notable for diffuse HSIL of the anal canal (Fig. 8.4a, b) as well as perianal condylomata. His anal lesions were not treated due to lack of patient follow-up. Six months prior to presentation he began to note worsening anal pain and "growing warts." Six weeks prior he was admitted for inpatient drug rehabilitation at which time he restarted ART. CD4 count at the time was 10 cells per microliter and viral load was >1 million copies per milliliter. The patient remained off recreational drugs after discharge and made arrangements for evaluation of his anal pain. His history was additionally notable for a 20 pack-year history of active tobacco use.

On initial exam the patient was afebrile and vital signs were stable. He was a slim and somewhat anxious, but otherwise well-appearing man in no acute distress. Inspection was notable for a large, tender ulcer with heaped-up edges that extended from the anal verge into the posterior perianus (Fig. 8.5). Circumferential subcutaneous lidocaine was liberally administered before further examination.

Digital anorectal exam (DARE) next revealed a firm, deep crevice extending from the posterior midline of the proximal anal canal tracking to the perianus. HRA confirmed the presence of a 4 cm ulcerated mass arising from the squamocolumnar junction (SCJ). Punch biopsies were consistent with invasive anal squamous cell carcinoma (SCC) and the patient was referred to oncology for staging and therapy.

The above patient had many risk factors for anal cancer including advanced HIV with low CD4 nadir, a history of multiple male sexual partners and tobacco use. Persistent anal pain should raise suspicion for malignancy. Firm ulceration, particularly when surrounded by heaped-up edges, is highly suggestive of invasive anal cancer. Definitive treatment with chemoradiation allows for preservation of bowel continence; fortunately, abdominoperineal resection is

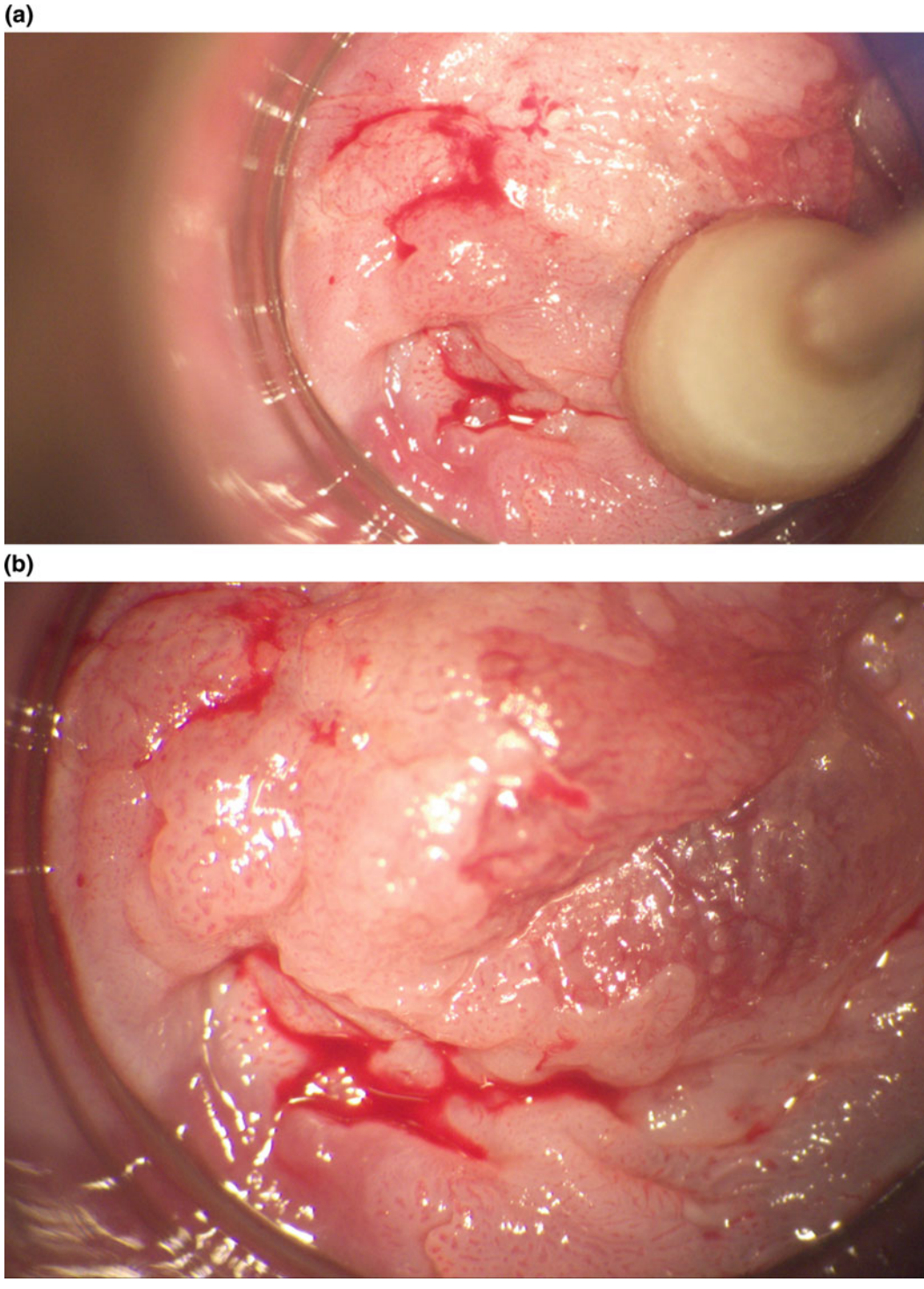

Fig. 8.4 Anal canal HSIL at low (**a**) and high (**b**) power magnification. Findings are notable for thick, sharply demarcated areas of acetowhite lesions with coarse punctuation and striated vessels

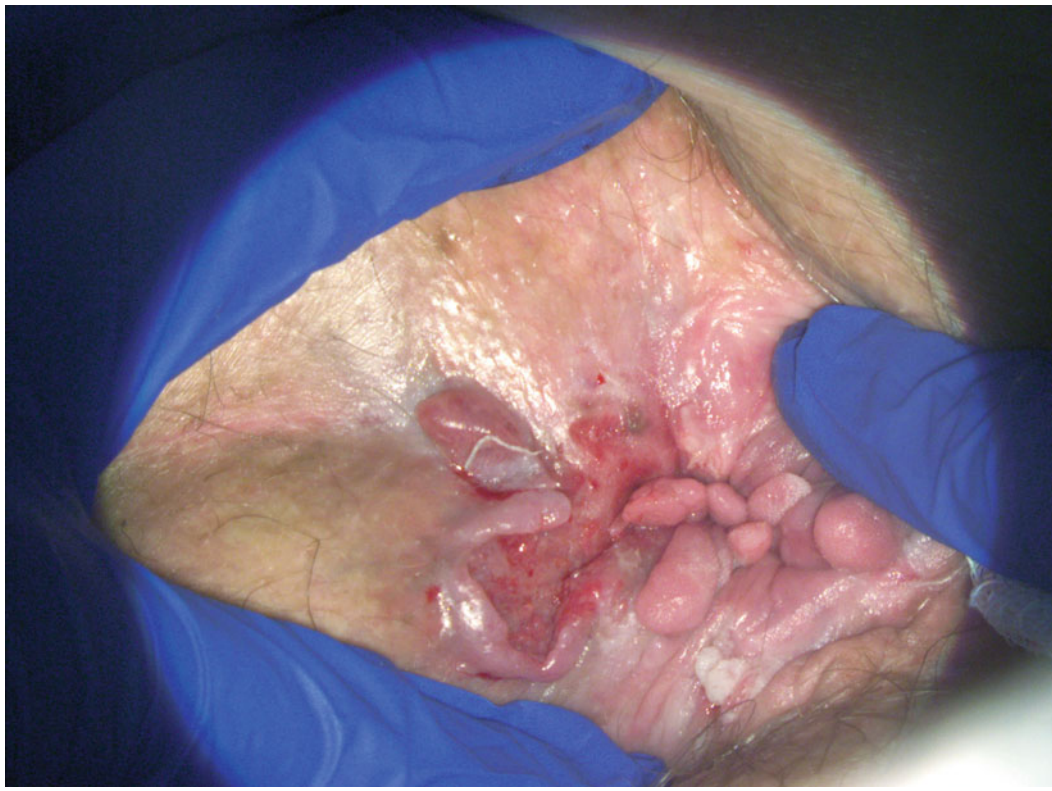

Fig. 8.5 Invasive squamous cell carcinoma of the anus. There are multiple perianal skin tags and condylomata. In addition, a large, posterior ulcerated lesion appears to track from the anal canal to the perianus. Its ulceration and heaped-up edges are consistent with invasive squamous cell carcinoma

usually not required. In this case, imaging showed no evidence of lymphadenopathy or distant metastases and the patient successfully completed chemoradiation for his stage 2 anal cancer with no evidence of disease recurrence at his most recent follow-up 2 years after diagnosis. The following sections comment on the epidemiology of HPV-associated malignancies in PLWH and discuss available methods to decrease their incidence.

Epidemiology of Anogenital HPV Infection in Men and Women with HIV

Initial cervical HPV infection occurs soon after sexual debut with prevalence peaking approximately 10 years later, followed by a gradual decline with increasing age [30]. While HPV infection of the anal canal also follows sexual debut, the prevalence of anal HPV infection is constant with age [31].

Risk factors for cervical HPV infection include early onset of sexual activity, a history of multiple sexual partners and history of other sexually transmitted infections [5]. The risk factors for anal HPV infection additionally include a history of anal receptive intercourse [9] and, for women, a history of cervical HPV infection or of cervical, vaginal or vulvar SIL or cancer [32–35].

The prevalence of cervical HPV in HIV-infected women is at least twice that of HIV-uninfected women with comparable sexual risk behaviors [36–39]. Similarly, the prevalence of anal HPV in HIV-infected men who have sex with men (MSM) is 95% [40, 41], compared with 57% in HIV-uninfected MSM [31]. The

prevalence of anal HPV infection is also higher in HIV-infected women and men who have sex with women (MSW) compared with their HIV-uninfected counterparts [42–44].

It is thus unsurprising that cervical and anal HSIL are also more common in both men and women living with HIV. Older studies show at least twice the prevalence of cervical HSIL in HIV-infected women compared with HIV-uninfected women [45]. The prevalence of anal HSIL in HIV-infected MSM is 50% compared with 25% in HIV-uninfected MSM [46, 47] while the prevalence of anal HSIL in HIV-infected women is 9% compared with 1% in HIV-uninfected women [42]. This effect is attributed to higher rates of both incident and persistent HPV infection and SIL [9].

Progression of HSIL to Invasive Cancer

The risk of progression to cervical cancer is high once cervical HSIL is present if left untreated. This is known from an unethical study from New Zealand in which cervical HSIL treatment was withheld [48]. The risk of invasive cervical cancer was 20% at 5 years and up to 50% at 30 years among women with HSIL who did not receive excisional therapy. The study also showed an average time of 10–15 years for progression of HSIL to invasive cancer [49]. The risk of and time to progression from cervical HSIL to invasive cancer specific to HIV-infected women has not been determined since treatment of cervical HSIL is standard of care.

Progression from anal HSIL to invasive anal cancer has likewise not been directly measured. However, data on HPV prevalence and anal cancer incidence were used to indirectly measure this rate in MSM, which was estimated to be 1 in 377 patients per year in HIV-infected MSM and 1 in 4196 patients per year in HIV-uninfected MSM [50]. Given the increased longevity afforded by ART, there may be as high as a 10% lifetime risk of anal cancer in HIV-infected MSM.

It is worth noting that on a per-HPV 16 infection basis the estimated rates of progression for anal HSIL are notably lower than the measured risk of progression to cancer for cervical HSIL (approximately 1 in 80 per year) [48], suggesting that anal HPV infection is less likely to lead to cancer than cervical HPV infection. The reason for the higher susceptibility of the cervix to malignant transformation compared with the anus is unknown, but may involve factors such as the hormonal milieu, and potentially the different microbiomes of the two sites.

Incidence of Cervical Cancer in PLWH

Until recently, efforts to prevent cervical cancer have relied primarily on use of the cervical cytology to identify (and subsequently treat) women at risk for cervical HSIL before progression to invasive cancer. The burden of cervical cancer today falls disproportionately in the developing world where such screening is not readily available. In the US the incidence of cervical cancer is 7.8 per 100,000 women-years [51], whereas the incidence in many areas of sub-Saharan Africa exceeds 40 per 100,000 women-years [52].

The main risk factor for cervical cancer is HPV infection and the risk factors for cervical cancer are therefore those associated with acquisition of HPV as previously described. Tobacco is an additional risk factor [53]. HIV infection has emerged as an additional important risk factor. In 1993, the Centers for Disease Control added invasive cervical cancer to the list of AIDS-defining malignancies, joining Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) [54]. This decision was controversial because only an increase in cervical SIL had been demonstrated in HIV-infected women at the time [55]. Subsequently, several large cohorts from the US and Europe showed standardized incidence ratios (SIRs) ranging from 5 to 10 for cervical cancer for HIV-infected women compared with the general population [56–59].

Data on the incidence of cervical cancer among HIV-infected women in lower income countries are more limited. Linkage of 15,000 HIV-infected individuals from Kyadondo

County, Uganda, to the county's cancer registry led to an estimated cervical cancer incidence of 70 per 100,000 women-years and a SIR of 2.7 compared with HIV-uninfected women [60]. There are also several case-control studies from sub-Saharan Africa and India in which patients with cancer were screened for HIV and the odds ratios (ORs) of exposure to HIV were calculated [61–63]. Results ranged from 1.1 to 7.9, however, the generalizability of these results is limited since they were derived from treatment centers instead of representative cohorts or registries.

Incidence of Anal Cancer in PLWH

Similar to cervical cancer, risk factors for anal cancer include tobacco and factors associated with sexual acquisition of anal HPV infection. As in the case illustration, these include history of multiple sexual partners, perianal warts, and/or receptive anal intercourse [64–66]. In the case of women a history of cervical, vaginal, and/or vulvar SIL or cancer are additional risk factors [67].

In addition to HPV, HIV infection and other forms of acquired immunosuppression have emerged as arguably the strongest risk factors for anal cancer. There is at least a 10-fold increase in incidence among HIV-infected women compared with HIV-uninfected women [56, 68–70] and a greater than 40-fold increase in HIV-infected men who only have sex with women (MSW) compared with their HIV-uninfected counterparts [69, 70]. MSM with HIV infection are at highest overall risk of developing anal cancer. The age-adjusted incidence in this group one of the most common malignancies in this population [51].

The markedly elevated risk of anal cancer in HIV-infected men is sufficient to partially account for the rising incidence of anal cancer in the US male population; excluding HIV-infected men, the annual increase in the incidence of anal cancer in the general population of men is 1.7%, whereas the annual increase is 3.4% when they are included [71]. The contribution of HIV infection to the incidence of anal cancer in the general population of women is not as clear, presumably due to the smaller number of HIV-infected women in the U.S. [72] and to the lower incidence of anal cancer in HIV-infected women compared with HIV-infected men. Data on the incidence of anal cancer in PLWH from lower income countries are sparse [73].

Effect of ART and Immune-Reconstitution

Low CD4 count is associated with cervical cancer risk in some [56, 57, 69] but not all studies [74]; interpretation is further confounded by the heterogeneity of CD4 endpoints (e.g., CD4 nadir vs. current CD4). For anal cancer, a low CD4 count nadir, particularly when present for a prolonged time, has been associated with risk of anal cancer in several studies [56, 57, 69]. One study also identified an association between anal cancer and low CD4 count at time of cancer diagnosis [75]. However, as in the case of cervical cancer, the association between low CD4 count and anal cancer is not universal [74].

It is hence unsurprising that immune-reconstitution due to ART shows some but by no means complete protection against HPV infection, HSIL, and invasive anogenital cancer. Although initial studies failed to demonstrate a protective effect of ART for either cervical [76, 77] or anal HPV infection [33], these studies were relatively small, had short follow-up intervals and were conducted early in the ART era when medication was less effective. More recently, large prospective cohorts note a modestly protective effect of HIV suppression against cervical HPV infection [78–81]. Likewise, a cross-sectional study of HIV-infected MSM reported a protective effect of ART against anal HPV infection [81]. The overall impact of this effect is uncertain given the high baseline prevalence of cervical and anal HPV infection in PLWH and the fact that many PLWH initiated ART at lower CD4 counts than is the current practice.

The evidence regarding the effect of ART on HSIL is limited since disease is often treated

once identified, although a longitudinal study that censored data after treatment of cervical SIL found that women on ART had three times the hazard of experiencing spontaneous cervical SIL regression [79]. Similarly, a second longitudinal study that adjusted for treatment of cervical SIL noted that women on ART had twice the hazard of regression of hr-HPV-positive SIL detected by cytology [78]. In the anus, a cross-sectional study of MSM showed that patients on ART were half as likely to have anal SIL [81].

As in the case of HPV infection, the moderate measures of association suggest that the impact of ART on SIL will be limited among patients for whom the baseline prevalence of disease is already high. Furthermore, the only recent study to evaluate the effect of ART on HSIL specifically (as opposed to SIL overall) found that MSM on ART for >4 years were less likely to develop anal HSIL (OR 0.28), but results were not statistically significant [82].

The effect of immune restoration with ART on cancer incidence is also unclear. While the incidence of KS and NHL declined quickly after the introduction of ART [55], the earliest post-ART data showed stable rates of cervical cancer [57, 68, 83]. More recent studies from the French Hospital Database on HIV and the US HIV/AIDS Cancer Match Study point to a decrease in incidence [59, 84], however, these data also reflect changes in screening practices and in the presence of modifiable risk factors such as tobacco use. The incidence of anal cancer has increased markedly in the post-ART area, although results vary on whether this rate continues to rise [57, 74, 84] or has plateaued [68, 69]. However, this increase in anal cancer incidence is largely attributed to the longevity of patients on ART who now live long enough to develop cancer rather than to a direct effect of ART.

Two recent studies attempted to measure the effect of ART on anal cancer while accounting for patient longevity. A case-control study nested within the Swiss HIV Cohort Study used incidence density sampling and matching to account for differences in follow-up time as well as in age and time period of cancer diagnosis [85]. This study found no association between the diagnosis of anal cancer and a history of (any) ART. However, it did not account for the presence or absence of virologic suppression or the duration of ART exposure. The second study is a retrospective cohort from the Veterans Affairs HIV Clinical Case Registry that examined the role of effective ART over time by comparing the incidence of anal cancer among men on ART with and without suppressed HIV viral loads [86]. Men who maintained a suppressed viral load had a lower incidence of anal cancer thus suggesting at least some protective effect of ART.

Thus, while risk of HPV-related malignancies is related to degree of immunosuppression, particularly as measured by CD4 nadir, the extent of protection conferred by ART and immune restoration is unclear. While cervical cancer incidence in HIV-infected women has decreased in the US and Europe, this is unlikely to be the case in the developing world, where screening for and treatment of cervical HSIL are not widely available. In comparison, the incidence of anal cancer has dramatically increased among HIV-infected individuals following the advent of ART. This difference may partly reflect the absence of widespread screening programs for anal cancer. Furthermore, because cervical cancer affects younger patients, the incidence of cervical cancer may be less affected than that of anal cancer by the increased longevity conferred by ART.

Cancer Characteristics and Treatment Outcomes

Cancer in PLWH occurs 10–20 years earlier compared with the general population [87]. Inflammation and early immune senescence have been hypothesized to result in premature aging leading to this effect. However, despite aging of the HIV-infected population, the proportion of older PLWH remains considerably smaller compared with the general population. This truncated distribution precludes the observation of cancers in older age groups and is now thought to account for much of this difference:

cervical and anal cancer only present 2–3 years earlier in PLWH compared with the general population after adjusting for differences in age distribution [59, 87]. While a direct effect of HIV may still be present, its magnitude appears much smaller than previously estimated.

While evidence suggests that PLWH present with more advanced cancer compared with the general population [88], it is unclear if this extends to cervical and anal cancer. This is because staging comparisons of individual malignancies are limited in power due to relatively small sample sizes. There is also little information on how PLWH tolerate cancer treatment because HIV infection is traditionally an exclusion criterion for cancer clinical trials although several retrospective cohorts do indicate that PLWH on antiretroviral therapy tolerate anal cancer chemoradiation similarly well compared with HIV-uninfected patients [89–91]. Data from registries does show that PLWH are less likely to receive cancer treatment for several malignancies [92, 93], suggesting differential access to health care and/or hesitancy to treat HIV-infected individuals.

Cervical cancer mortality is elevated in US PLWH compared with the general population, even after accounting for differences in stage and likelihood of obtaining therapy [88]. However, because cancer registries provide limited treatment information (e.g., data on completion of therapy are missing), it is premature to attribute elevated cancer-specific mortality to HIV itself rather than to underlying differences in therapy. Mortality for anal cancer in US PLWH does not appear elevated compared with the general population although data from cohort studies are limited by low sample size [91, 94].

Cervical and Anal Cancer Prevention in PLWH

Two distinct approaches exist to decrease HPV-related malignancies. Until the last decade, preventative efforts consisted of screening tests to detect and subsequently eliminate HSIL before progression to invasive cancer. The year 2006 marked the introduction of HPV vaccination, which effectively prevents initial HPV infection with vaccine HPV types before HSIL can be established. Both methods represent important and complementary tools to decrease the risk of complications related to HPV.

Cervical HSIL Screening

Screening tests detect disease that is already established. To be of value, a screening test should help detect disease at a sufficiently early point in its natural history to provide substantial benefit [95].

The cervical Papanicolaou (Pap) smear, or cervical cytology, was developed by George Papanicolaou and implemented in the US in the early 1940s to detect both cervical cancer and precancerous lesions like HSIL, and is still widely used today [96]. Women with abnormal cytology are referred for colposcopy, where a colposcope microscope and acetic acid are used to examine the cervix and identify HSIL. Affected areas are typically removed by loop electroexcisional procedure (LEEP), which can be done in the office, or cone conization, which is performed in the operating room [5]. Although no randomized-controlled trials exist to establish the efficacy of cervical cytology screening and treatment of HSIL, the rapid drop in US cervical cancer incidence after the 1940s provides compelling evidence of its effectiveness [96].

The advent of molecular techniques to test for hr-HPV has further improved the sensitivity and specificity of cervical cancer screening. Hr-HPV testing can be performed as a “reflex test” (in response to an abnormal cervical cytology), a “co-test” (automatically with cervical cytology) or as a primary stand-alone test. US guidelines from 2011 recommend cervical cytology every 3 years with the option of using reflex hr-HPV to determine who should undergo colposcopy when cytologies show atypical squamous cells of undetermined significance (ASC-US). In addition, co-testing can be used in women

≥30-years old to extend the screening interval to every 5 years when both cervical cytology and hr-HPV testing are negative [97].

Interim guidelines from 2015 additionally include the Roche Cobas® HPV test as an alternate primary screening modality in women ≥25-years old [98], following the publication of both a US prospective cohort documenting its high sensitivity in detecting cervical HSIL [99] and of several randomized-controlled European studies showing lower cervical cancer incidence when hr-HPV testing is used as a primary screening tool compared with cytology alone [100]. Of note, the high sensitivity of the Cobas® HPV test also results in a greater number of colposcopies including among women aged 25–30 for whom the absolute risk of invasive cervical cancer remains very low [98]; it is still unclear whether the additional identification of HSIL actually translates into a meaningful reduction of cervical cancer within this age group.

Recently, the Women's Interagency HIV Study showed that cytology and HPV co-testing is also specifically effective in HIV-infected women [101] and as of 2015 its use is incorporated into the screening algorithm for HIV-infected women recommended by the Centers for Disease Control and Prevention, the National Institute of Health and the HIV Medicine Association of the Infectious Diseases Society of America (HIVMA) [102].

These guidelines recommend screening with cervical cytology starting within 1 year of sexual activity but not later than age 21 years. For women aged 21–29 years with normal results, cytology can be repeated at 6 months (optional recommendation) and should be repeated at 12 months. Screening interval can subsequently be extended to every 3 years if all results are within normal limits. omen aged 21–29 with ASC-US can undergo reflex hr-HPV testing; if negative, cytology is repeated at 6–12 months. Women aged 21–29 years with LSIL, HSIL, ASC-H, hr-HPV-positive ASC-US, or persistent ASC-US on at least two cytologies are referred to colposcopy.

Yearly screening is recommended for HIV-infected women ≥30-years old, however, co-testing can be used to extend the interval to every 3 years when both cervical cytology and hr-HPV testing are negative. While screening can stop at age 65 years in low-risk HIV-uninfected women, cervical cancer screening is continued throughout the lifetime of HIV-infected women. There is presently no recommendation to use the Cobas® HPV test as a primary screening tool in HIV-infected women.

As described previously, the burden of cervical cancer presently resides disproportionately in lower income countries where the prevalence of HIV is high and where use of the Pap smear is difficult due to absence of the healthcare infrastructure to obtain and interpret cytologies, perform colposcopy to biopsy suspicious lesions, and then treat cervical HSIL. "Screen and treat" programs are an alternative method in which treatment is provided immediately or soon after a positive screening test [103]. Initial screening tests include direct visual inspection of the cervix with acetic acid (VIA) and/or Lugol's iodine (VILI) or hr-HPV testing. Simple lesions detected on VIA or VILI are treated immediately, typically with cryotherapy. More complex lesions that extend into the cervical canal or are suspicious for malignancy require further work-up including referral for LEEP or surgical excision. When hr-HPV testing is used, women with positive tests undergo similar cervical visualization and treatment of lesions once results are available.

The efficacy of such approaches is documented by several studies, including a large trial of largely HIV-uninfected South African women who underwent both visual inspection and hr-HPV testing and were subsequently randomized to one of three groups: cryotherapy if the hr-HPV test was positive, cryotherapy if visual inspection was positive (regardless of hr-HPV result) or no immediate treatment [104]. All three groups underwent follow-up colposcopy at 6 months at which point residual lesions were treated. Both cryotherapy arms resulted in sustained decreases in the detection of HSIL even at 36 months of follow-up (HSIL detection 1.5% for hr-HPV group vs. 5.6% for control group, $p < 0.001$ and HSIL detection 3.8% for

visualization group vs. 5.6% for control group, $p = 0.002$) [105]. The World Health Organization (WHO) has since published official "screen and treat" guidelines [103] and programs are being implemented in multiple lower income countries [106–109]. Hr-HPV is the preferred screening test but direct visualization is recommended when hr-HPV testing is unavailable due to cost and infrastructure requirements [103]. While only the Cobas® HPV test is approved for primary screening in the US, the WHO guidelines do not restrict the type of hr-HPV test for "screen and treat" programs.

Whether "screen and treat" programs specifically decrease HSIL or cervical cancer in HIV-infected women is unknown. However, several observational studies reflect the feasibility and ability of "screen and treat" programs to identify and treat cervical HSIL in HIV-infected women [110, 111]. Given the absence of cytology-based screening program in many countries where HIV infection is highly prevalent, it is necessary to encourage HIV-infected women from these regions to participate in "screen and treat" programs.

Anal HSIL Screening

There is great interest in the early detection of anal HSIL among HIV-infected individuals, particularly MSM [9]. Analogous to the cervical Pap smear, anal cytology can be used to identify individuals requiring further evaluation. To obtain an anal cytology, a Dacron swab is moistened with water and gently inserted into the anal canal until it hits the wall of the rectum. The swab is then extracted while rotating it in a spiral motion and gently applying mild pressure to the anal wall, after which it is immersed in preservative solution [112]. Slow extraction of the swab over 20 seconds helps ensure that an adequate sample is collected. To further increase cellular yield, vigorous agitation of the swab in preservative solution for at least 30 seconds is recommended. Digital anorectal examination (DARE) is performed following anal cytology to detect palpable, early invasive cancers. DARE should not be performed before anal cytology since the use of lubrication will interfere with anal cytology sampling.

The presence of any abnormality on DARE or anal cytology is typically followed by referral for HRA (Fig. 8.6). HRA involves use of a colposcope, the same instrument used to examine the cervix, to carefully examine the anal canal and perianus following the application of 5% acetic acid. The colposcope provides magnification and light while acetic acid leads to dehydration of the intracellular compartment making cells more refractive to light. Lesions suspicious for HSIL or malignancy are biopsied. Treatment of anal HSIL differs from cervical HSIL in that deep excision of the anal canal causes significant morbidity and is not generally feasible. Instead, therapy typically involves superficial ablation with electrocautery (hyfrecation) or infrared coagulation. These can usually be performed in the office with local anesthesia. Alternatively, topical 5-fluorouracil can be applied to the anal canal and/or perianus for patients with widely diffuse disease. Surgical excision is reserved primarily for diagnosis of suspected malignancy [10].

Several studies have compared anal cytology with same-day HRA to describe the test characteristics of anal cytology in HIV-infected MSM [113–119]. Results from studies specific to HIV-infected MSM are summarized in Table 8.1. Low specificity and positive predictive values (PPV) reflect the use of any cytological abnormality as the threshold for referral. Increasing the cytological severity required for referral would improve these values albeit at the expense of sensitivity and negative predictive value (NPV). Reported NPVs range from 70 to 90%. While a negative cytology therefore does not completely exclude anal HSIL, this approach is generally acceptable given the slow progression of anal HSIL such that overall NPV can increase by performing serial cytologies in a given patient over time. As an alternative, some propose direct referral for HRA without cytology for high-risk groups [120]; however, the

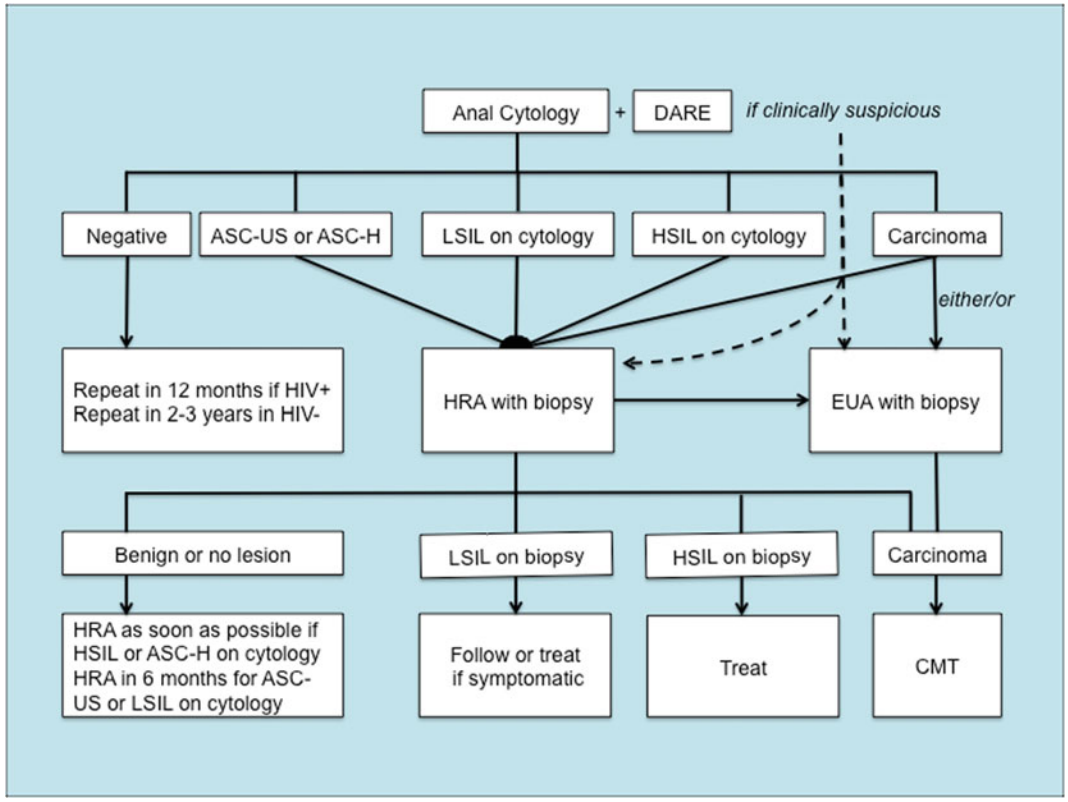

Fig. 8.6 Anal cancer/HSIL screening algorithm. *ASC-US* atypical squamous cells of undetermined significance, *ASC-H* atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion, *CMT* combined modality therapy, *DARE* digital anorectal examination, *EUA* examination under anesthesia, *HRA* high-resolution anoscopy, *HSIL* high-grade intraepithelial lesions, *LSIL* low-grade squamous intraepithelial lesions. Adapted from [143]

Table 8.1 Performance of anal cytology in the detection of anal HSIL for HIV-infected MSM

Study	No	Sensitivity (%)	Specificity (%)	Positive predictive Value (%)	Negative predictive value (%)
Palefsky [119]	406	69	59	38	84
Berry [113]	35	87	47	57	82
Salit [114]	401	84	39	31	88
Wentzensen [115]	363	89	39	31	92
Phanuphak [116]	123	24	92	39	84
Sendagorta [117]	101	83	41	55	73
Jin [118]	213	84	47	54	79

feasibility of this approach is unclear given the limited availability of HRA. Hr-HPV co-testing adds little discriminatory power to anal cytology samples because of its exceedingly high prevalence among high-risk groups [120]. We do not presently recommend routine hr-HPV testing of the anal canal.

Ultimately, the optimal approach for anal cancer prevention in HIV-infected patients is unclear, largely because there are no conclusive studies to show that early detection and treatment of anal HSIL decrease the incidence of anal cancer. To address this, a large multisite randomized-controlled trial, known as the Anal Cancer/HSIL Outcomes Research (ANCHOR) Study is underway [121]. Presently the HIVMA recommends yearly anal cytology for the following HIV-infected patients: MSM, women with a history of receptive anal intercourse and any individual with genital warts [122]. The age to initiate screening is not specified. The New York State Department of Health is the only other health organization to recommend anal HSIL screening and it recommends routine anal cytology to similar HIV-infected subgroups regardless of age: MSM, women with a history vulvar or cervical SIL and individuals with a history of anogenital warts [112]. At UCSF we recommend delaying screening of asymptomatic HIV-infected MSM until age 25 years given the low incidence rates of anal cancer below 25 years. We recommend initial screening for at-risk HIV-infected women and heterosexual men at age 35–40 years.

It is worth noting that the presence of any cytological abnormality among HIV-infected patients is 63.1% for MSM [50], 38% for women [43] and 36% for heterosexual men [44]. Therefore, a substantial proportion of HIV-infected individuals will require further evaluation when cytology-based screening is offered. Before cytology is performed, patients should be counseled about the high probability of referral for HRA as well as the potential risks and benefits of treating anal HSIL. Cytology should not be performed if the infrastructure to identify and treat anal HSIL is unavailable. Here, we recommend at least yearly DARE to detect early palpable invasive anal cancer given the safety and feasibility of this approach.

Prophylactic HPV Vaccination

There are currently three different vaccines available to prevent initial HPV infection. All three contain virus-like particles (VLP) made up of recombinant L1 capsid subunits but differ in the types they cover. Standard vaccination includes a total of three vaccine doses administered at 0, 1–2 months and 6 months [123]. Vaccination generates high levels of neutralizing anti-L1 VLP antibodies, which prevent HPV attachment to the basal cell membrane, and thus, initial infection [2].

The first HPV vaccine was approved in 2006. Gardasil® is a quadrivalent vaccine (HPV4) produced by Merck & Co that confers protection against hr-HPV types 16 and 18 (responsible for 70% of cervical cancers and 85% of anal cancers [7]) and low-risk HPV types 6 and 11 (responsible for 90% of genital warts [8]). Two large, randomized-controlled trials in young women demonstrated excellent efficacy of HPV4 in preventing type-specific cervical HSIL and genital warts in the per-protocol analysis (98 and 100%, respectively) [124, 125]. The per-protocol analysis included women who remained HPV-negative 1 month after completion of the vaccination series; efficacy was lower in the intention-to-treat analysis (44% for cervical HSIL and 73% for anogenital warts). In 2009, GlaxoSmithKline introduced a bivalent vaccine (HPV2), Cervarix®, which protects against HPV 16 and 18. Its efficacy against type-specific cervical HSIL is comparable to HPV4 [126].

The lower efficacy in the intention-to-treat analyses highlights a key characteristic of prophylactic HPV vaccines: they work when administered *prior* to HPV exposure. Because initial HPV infection occurs soon after sexual debut [30, 31], vaccination is most effective when given before recipients are sexually active. The US Advisory Committee on Immunization Practices (ACIP) consequently recommended routine vaccination with either HPV2 or HPV4

of females 11–12-years old, with immunization starting as early as age 9 years and extending through age 26 years [127, 128]. In 2011, the ACIP additionally recommended routine HPV4 vaccination of heterosexual males through age 21 years and of MSM through age 26 years [129] following studies that established its efficacy in genital wart prevention among young men [130], and anal HSIL prevention in MSM [131]. Recommended vaccination was also extended to immunocompromised individuals, including those with HIV infection, through age 26 years based on safety and immunogenicity studies within these populations [129].

Merck introduced a nonavalent vaccine (HPV9), Gardasil®9, in 2014. In addition to covering strains 6, 11, 16, and 18, HPV9 confers additional protection from hr-HPV types 31, 33, 45, 52, and 58 [132]. Presently, females may receive any of HPV2, HPV4, or HPV9 while males can receive either HPV4 or HPV9. Routine HPV vaccination should be initiated at age 11–12 years but can be started as early as 9 years. "Catch-up" vaccination is recommended for females aged 13 through 26 years and for males through 21 years. As with HPV4, vaccination with HPV9 for males is further extended through age 26 for MSM and immunocompromised males. Use of the same HPV vaccine (e.g., HPV2, HPV4, or HPV9) across all three vaccine doses is preferred but not strictly necessary [123].

HPV Vaccine Uptake

High-income countries, such as Australia, Denmark, and England have established successful vaccination programs and achieved administration of three doses of HPV vaccine in $\geq 70\%$ of targeted individuals [133]. Post-licensure monitoring studies show sharp reductions in the incidence of genital warts, vaccine-specific HPV infection, and cervical HSIL, thus establishing vaccine effectiveness outside of clinical trials [133].

Vaccine uptake has been less widespread in the US. In 2006, the CDC created the National Immunization Survey-Teen (NIS-teen) in response to new ACIP recommendations for HPV vaccination and two additional adolescent vaccines: quadrivalent meningococcal polysaccharide-protein conjugate vaccine (MCV4) and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) [134]. By 2010, only 48.7% of female adolescents had received ≥ 1 dose of HPV vaccine compared with 62.7% for MCV4 and 81.2% for Tdap in male and female adolescents [135]. Improvements were noted in 2014; however, vaccination rates still lag behind those of MCV4 and Tdap (60% of females and 41.7% of male adolescents had received ≥ 1 dose HPV, compared with 79.3 and 87.6% for MCV4 and Tdap, respectively) [136]. The US Census Bureau's National Health Interview Survey shows similarly low HPV vaccine uptake in adults: 40.2% eligible women and 13.0% of eligible males had received ≥ 1 dose HPV by 2014 [137].

Low HPV uptake in the US is linked to limited knowledge among healthcare professionals and parents. Many healthcare professionals are less likely to recommend the HPV vaccine to younger patients and often recommend it based on the perceived risk rather than before the onset of sexual activity [138]. This results in missed clinical opportunities: that is, provider visits where at least one other adolescent vaccination is received. It is estimated that eliminating missed clinical opportunities alone would result in coverage rates of 80–90% for the first HPV dose, highlighting the need for active educational programs to increase provider and caregiver knowledge [139].

Cost is the largest barrier to HPV vaccination in lower income countries. The Pan American Health Organization has facilitated introduction of the HPV vaccine in Central and South American middle-income countries, whereas the Global Alliance for Vaccines and Immunizations is helping implement national programs in low-income countries where the infrastructure for countrywide programs exists, or demonstration projects when national platforms are unavailable [133]. Figure 8.7 shows countries with national HPV vaccination programs.

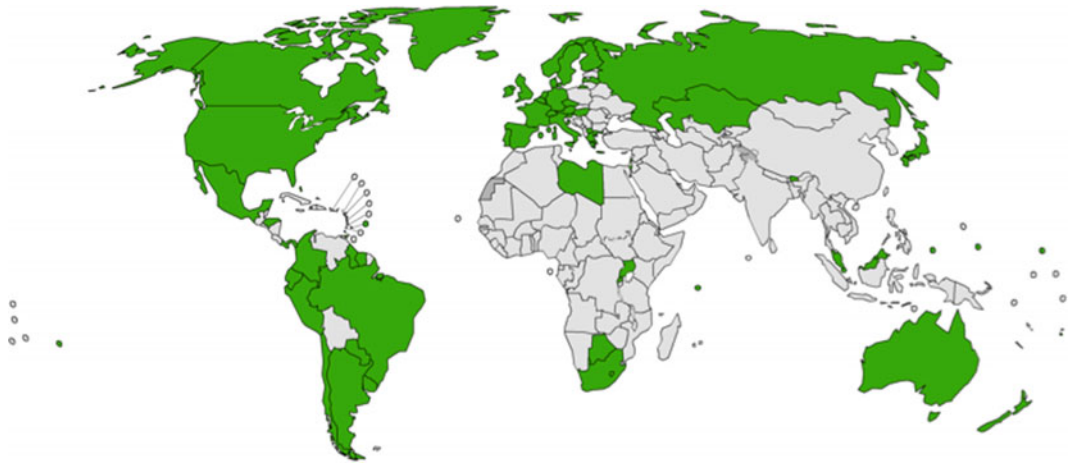

Fig. 8.7 Countries with HPV in the national immunization program as of September 5, 2016. In *green*: 67 countries (34.5%) with national HPV immunization programs. In *gray*: 127 countries (65.5%) do not have HPV national immunization programs (Reprinted from [144]

There is a paucity of data on HPV vaccine uptake among HIV-infected individuals in both high and lower income countries. However, timely implementation of widespread HPV vaccination offers an excellent opportunity to decrease the burden of HPV disease among young and newly HIV-infected individuals. This is particularly relevant in lower income countries where the prevalence of HIV is high and the infrastructure for cervical and anal cancer screening is not readily available.

Conclusion

The increased life expectancy of PLWH has led to a growing interest in the prevention of long-term complications from HIV infection, including HPV-related malignancies. Although preventable, cervical cancer still causes substantial morbidity and mortality in lower income countries where national screening programs are unavailable. Anal HSIL screening is not widely available due to limited availability of HRA-trained providers and the absence of data conclusively establishing its effectiveness. Although prophylactic HPV vaccines offer an excellent means to prevent HPV disease, their short-term impact is limited by relatively low vaccine uptake and absence of an effect in individuals already exposed to HPV. Fortunately, screening for prevention of both cervical and anal cancer in PLWH are areas of active interest and research. See-and-treat programs to prevent cervical cancer are actively being implemented in many lower income countries, while results from an ongoing, large, randomized-controlled trial of anal HSIL treatment should establish the efficacy of anal cancer prevention efforts and help implement guidelines on how to treat anal HSIL among PLWH [121].

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Bacterial Vaginosis

9

Jack D. Sobel

Introduction

Bacterial vaginosis (BV) is the most prevalent vaginal infection in women of reproductive age, characterized by a profoundly disturbed vaginal microbiota dominated by variable communities of anaerobes including *Gardnerella vaginalis*, *Atopobium vaginale*, and *Prevotella* species [1, 2].

Although mostly an asymptomatic syndrome, symptoms when present, especially when frequently recurring, are themselves extremely troublesome and underestimated by most authors [1–3]. However, BV is especially important because of associated adverse outcomes both obstetric and gynecologic.

Women with BV are at increased risk for chorioamnionitis, preterm delivery and prematurity as well as development of infection with herpes simplex virus type 2, *Trichomonas vaginalis*, *Neisseria gonorrheae*, and *Chlamydia trachomatis* [4–7]. Most importantly, however and relevant to this textbook, BV is also associated with an increased risk of human immunodeficiency virus (HIV) acquisition and transmission [8, 9]. A list of obstetric and gynecologic complications of BV is seen in Table 9.1. The purpose of this chapter is to review BV in the context of HIV and will not focus on pregnancy issues, specifically prevention of prematurity and preterm labor.

Epidemiology

Worldwide BV is the most prevalent vaginal infection in women of reproductive age, unknown in prepubertal females and rare in estrogen deficient postmenopausal women, affecting approximately 20% of women in the general population and 50% of African American woman [1, 10]. An extensive global epidemiologic review by Kenyon et al. [1] concluded that BV prevalence varied considerably between ethnic groups in North America, South America, Europe, the Middle East and Asia, being highest in parts of Africa and lowest in much of Asia and Europe, especially in its western regions. The large differences in BV prevalence by ethnicity and geographical region remains incompletely understood especially given the large numbers of individual level risk factors reported. The difficulty in explaining these epidemiologic differences are compounded by two critical factors. First, BV does not exist as a single entity such as gonorrhea or trichomoniasis in that this syndrome is associated with several variant bacterial subtypes reflecting significant differences in microbiota composition [11]. In addition,

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Table 9.1 Obstetric and gynecologic complications of BV

Obstetric
Chorioamnionitis
Premature rupture of membranes
Preterm labor/delivery
Low birth weight
Amniotic fluid infection
Postpartum endometritis
Gynecologic
Tubal infertility
Pelvic inflammatory disease
Postabortal pelvic inflammatory disease
HIV transmission/acquisition/susceptibility
Postsurgical infection
Urinary tract infection
Cervical intraepithelial neoplasia
Mucopurulent endocervicitis
Strong association with STDs (e.g., trichomoniasis, gonorrhea, chlamydia, herpes simplex virus, human papillomavirus)

occurrence of BV may reflect first episode (i.e., primary infection), or recurrence of BV which may have entirely different pathogenetic mechanisms.

Basic Science Considerations Relevant to Bacterial Vaginosis

There is a growing consensus that BV is primarily a sexually transmitted infection (STI) based on data originating from lesbian couples as well as numerous heterosexual-based studies [12, 13]. Earlier conflicting studies reporting the presence of BV in virgin females have not stood the test of time [14]. This should not imply that all of the frequently recurring episodes of BV are due to sexual reexposure and reinfection although some undoubtedly are. Similarly, this observation in no way implies that there is a necessity to treat male sexual partners since proof of efficacy is entirely absent [15]. Support for heterosexual transmission was initially based upon epidemiologic studies including findings such as numbers of, or recent change in sexual partners as predictors of BV, but has been fortified by laboratory studies confirming the presence of major BV pathogens in a biofilm within the male urethra or under the penile prepuce [16]. Therefore, while no clinical treatment trial exists at this time to support treatment of male partners, this topic certainly deserves further study.

A variety of other risk factors influencing pathogenesis of BV are reported include douching, black race, intrauterine device, smoking, menses, lack of male circumcision, low vitamin-D levels, dietary factors, and likely genetic factors [17–19]. The use of hormonal contraception is reported to be associated with a decreased incidence of BV including recurrent BV (RBV) [20].

For several decades the microbiology of BV has been established with BV recognized as a form of microbial dysbiosis with massive overgrowth of several anaerobic bacterial species, and accompanying depletion and disappearance of normal if not dominating *Lactobacillus* species viz *L. crispatus*, *L. jensenii*, and *L. gasseri*. High titers of *G. vaginalis*, *Prevotella* species and a variety of *Mycoplasma* species were consistently reported and thought to be responsible for the malodorous vaginal discharge.

The introduction of molecular techniques allowed the recognition of numerous uncultivatable previously unrecognized anaerobic bacterial species including *Atopobium vaginae*, *Megasphaera* species, and multiple additional species including *Clostridial* species [21–23]. While knowledge of these multiple species has facilitated new diagnostic tests for BV, little light has been shed on the pathogenesis of BV, although microbiome analysis may facilitate prediction of recurrence after seemingly successful antimicrobial therapy. Most importantly, microbiome studies indicate lack of bacterial uniformity in women meeting screening diagnostics currently used (i.e., Nugent score and Amsel criteria), which although proven to be useful are extremely nonspecific with regard to microbial composition [24]. Accordingly, there is now recognition that

BV constitutes a syndrome of varying bacterial community types [11]. This explains variable rates of complications, response to therapy and relapse.

One bacterial species, *G. vaginalis*, is currently favored as the most likely pathogen that may serve as a single "trigger" in the pathogenesis of BV. For instance, *G. vaginalis* is almost always present in microbiome studies in BV and at titers several logs greater than its population numbers when colonizing women without BV. This theory is reinforced by several reports of the existence of a bacterial biofilm coating the epithelial surface of the vagina and not found in healthy women [16]. The biofilm serves as a reservoir or sanctuary for multiple bacterial pathogens predominantly *G. vaginalis*.

A similar biofilm is reported to coat the epithelial surface of the male urethra and contained therein is *G. vaginalis*, observations supporting the concept of heterosexual transmission and focusing on *G. vaginalis* as the likely trigger [16]. In addition, recent genetic studies indicate several clades of *G. vaginalis*, which vary in terms of virulence potential and antimicrobial susceptibility. Biofilm recognition is now the most plausible explanation for pathogen persistence in the face of antibiotic therapy and the basis for recurrent symptomatic relapses in celibate women. Moreover, recognition of biofilm has initiated a new generation of therapeutic measures to be used in conjunction with antibacterials. Recent studies suggest that Herpes Simplex virus type 2 infection is an important BV risk factor [25] whereas prevalent BV may lead to increased risk of HSV-2 acquisition.

Bacterial Vaginosis in HIV-Infected Women

HIV infection has been shown to be more frequent in women with BV than those without BV. In addition, HIV infection is associated with increased occurrence of BV [26, 27]. In studies evaluating incident HIV, BV was associated with a 1.61-fold increased risk of HIV acquisition [8]. Elevated pH due to absence of lactobacilli, changes in cytokines, loss of other normal flora protective substances, decreased secretory leukocyte protease inhibitor: all may contribute to enhanced susceptibility [28–34]. BV has been associated with a 60% increased risk of HIV-1 acquisition in women and higher concentration of HIV-1 RNA in the genital tract. BV is reported to be present in up to half of African HIV-1 infected women and BV is responsible for increased risk of HIV-1 transmission (3 fold) to male partners and has been considered responsible for a substantial proportion of new HIV-1 infections in Africa [9].

Transmission of HIV-1 in the absence of cofactors is poorly efficient. There is substantial evidence that STIs including BV increase the likelihood of both acquiring and transmitting HIV [35, 36]. In this context, BV serves as a cofactor to enhance HIV transmission and normal vaginal microbiota play a protective role against acquisition of HIV [37].

HIV-positive women demonstrate increased risk of HIV shedding through a variety of mechanisms. This enhanced HIV shedding is significantly increased in women with BV and further increased with BV and trichomonas co-occurrence [38]. Co-occurrence of *T. vaginalis* and BV, although not infrequent in HIV-negative women, is significantly enhanced in HIV positive women [39], moreover women with BV appear to be at higher risk of acquiring trichomoniasis [40]. This synergy is likely related to intensified localized inflammation of the genital tract [41, 42]. In contrast, vaginal *Lactobacillus* spp are associated with lower risk of genital HIV-1 shedding, while a variety of BV-associated species increase risk of shedding [30, 33, 43]. In particular, Mitchell et al. [43] reported that the highest risk of HIV-1 RNA shedding was associated with BVAB3, *Leptotrichia* and *Sneathia* spp.

Level of expression of HIV in vaginal fluid is a critical factor in female to male transmission of HIV. So what explains this link between BV and rates of HIV infection and expression? Although BV has classically not been associated with signs of inflammation (i.e. increased white blood cells) in the vaginal discharge, nor with the

presence of pain, tenderness or erythema, markers of inflammation are present. These include pro-inflammatory cytokine and immune cell change. BV is associated with higher vaginal concentration of IL-1 beta, TNF, gamma-interferon, IL-2, IL-4, IL-6, and IL-10 [29]. Interferon gamma induces macrophage activation which may increase susceptibility to HIV infection. In addition IL-2 induces T and B lymphocytes also potentially increasing HIV susceptibility and levels in the genital tract [44]. The anti-inflammatory cytokines IL-4 and IL-10 are also increased in BV, potentially limiting inflammation as generally recognized. In particular IL-8, a potent polymorphonuclear leukocyte chemoattractant is not increased in BV explaining absence of such cells in BV. All in all, these genital mucosal inflammatory changes may explain the increase risk for HIV infection.

A Case

A 35-year-old female patient with well-controlled HIV presented to clinic for an urgent care appointment. She complained of an increased vaginal discharge of one week duration along with a "bad smell." Her menstrual cycle, which she characterized as normal, ended 2 weeks prior to presentation. She reported one male sexual partner over the last 12 months and inconsistent condom use. She felt that her current symptoms were consistent with symptoms that she had experienced in the past when she was diagnosed with a "vaginal infection." Review of her medical record revealed that she was diagnosed with bacterial vaginosis six times in the last twelve months and that at least three of the four Amsel criteria were satisfied at the time of each evaluation.

Physical examination revealed an adherent, white, homogeneous vaginal discharge present at the introitus and noted to be heavy upon speculum insertion. The vaginal tissues appeared normal. Vaginal pH = 7 and the "whiff" test was positive. The wet mount revealed many clue cells and the absence of white blood cells, trichomonads, and yeast forms. The patient was treated with oral metronidazole along with topical boric acid followed by a transition to 6 months of intravaginal metronidazole. The importance of consistent condom use was discussed. Specific aspects of this case will be covered further below.

Clinical Presentation

Approximately 50% of women with BV are asymptomatic. Dominant symptoms include a malodorous discharge. The discharge is described as white or grayish white with a fishy smell. Other less common symptoms include pruritus and irritation. Genital malodor is most detectable in the post-menstrual period and following intercourse. BV is not associated with dyspareunia or genital soreness although complaints of lower abdominal pain are not uncommon.

Physical examination reveals a strikingly normal appearing vulva and perineum, with or without a visible adherent whitish gray discharge. The vestibule, vagina and cervix have normal appearances with a discharge of variable volume evident in the vagina and which is frequently frothy (Fig. 9.1). Bimanual pelvic examination is usually normal.

Infrequently one finds a mixed infection due to BV and *Candida* species in which clinical features of both entities are evident. In contrast, mixed infections consisting of BV and trichomoniasis are extremely common [39].

Diagnostic Considerations

It should be emphasized that clinical criteria alone are not reliable in diagnosis. BV should never be diagnosed on clinical appearance alone. The Amsel criteria (Fig. 9.2) provide the cornerstone of the clinical diagnosis of BV in most practice settings. As part of the Amsel criteria, the following two bedside rapid tests serve as most valuable in rapid diagnosis. An elevated pH (pH > 4.5) is extremely useful and normal vaginal pH measurement virtually rules out BV. Similarly, a positive amine or "sniff" or "whiff"

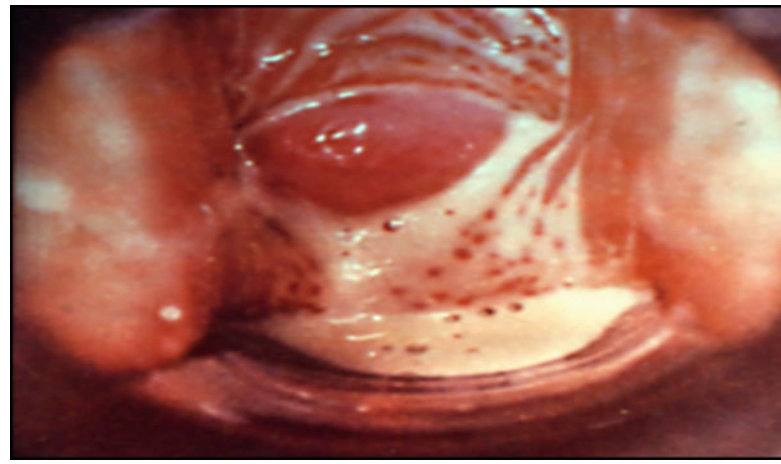

Fig. 9.1 Homogeneous vaginal discharge typical for bacterial vaginosis

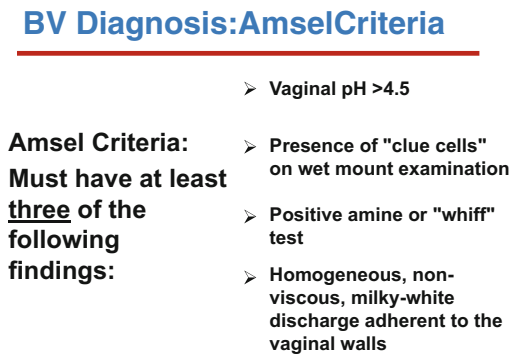

Fig. 9.2 Amsel criteria. Adapted from [61]

test provides immediate diagnostic confirmation following addition of a drop of 10% KOH to the vaginal swab. Before commencing microscopy, therefore, three of the four Amsel criteria have been evaluated (i.e., the presence of a homogeneous vaginal discharge, pH > 4.5 and positive "whiff" test). The purpose of saline microscopy is to detect the presence of clue cells, the most specific of the four Amsel factors. However, saline microscopy affords the observer the opportunity to explore the presence of yeast blastospores and hyphae as well as motile trichomonads. Two additional benefits include evaluating the presence or absence of polymorphonuclear leukocytes, which are invariably present in trichomoniasis and absent in BV and finally to view bacterial morphotype present between the squamous cells. In BV the striking feature is the absence of rod-like *lactobacillus* bacillary morphotype replaced by coccobacillary organisms (Fig. 9.3a–d).

Unfortunately pH measurement and microscopy are essential steps that have disappeared from widespread clinical use. Clinicians most frequently guess and use clinical criteria or perform additional less labor intensive tests. The most frequently performed rapid test is the sialidase test [i.e., OSOM® BVBLUE® test (Sekisui Diagnostics, Lexington, MA)], which has disappointing results with reported sensitivity and specificity of 88–99% and 91–98%, respectively [45]. Most practitioners resort to 'send out' tests. The most widely used is the BD Affirm™ VPIII test (BD Diagnostics, Sparks, MD) which uses DNA homology probes to diagnose *Gardnerella*, *Candida* and *Trichomonas*. Results are usually available in under an hour though may take longer, depending on the lab reporting mechanism. The BD Affirm™ test is extremely sensitive resulting in BV overdiagnosis in some situations due to heightened sensitivity in detecting normal levels of *G. vaginalis*. A negative BV probe reliably rules out BV. This test should not be used for test of cure assessment.

In the last few years, several commercial diagnostic companies have emerged using extremely sophisticated PCR molecular methods that detect and quantitate a number of target anaerobic bacterial species, usually *A. vaginae*, *Megasphaera*, and BVAB [46]. Some but not all commercially available diagnostic tests have

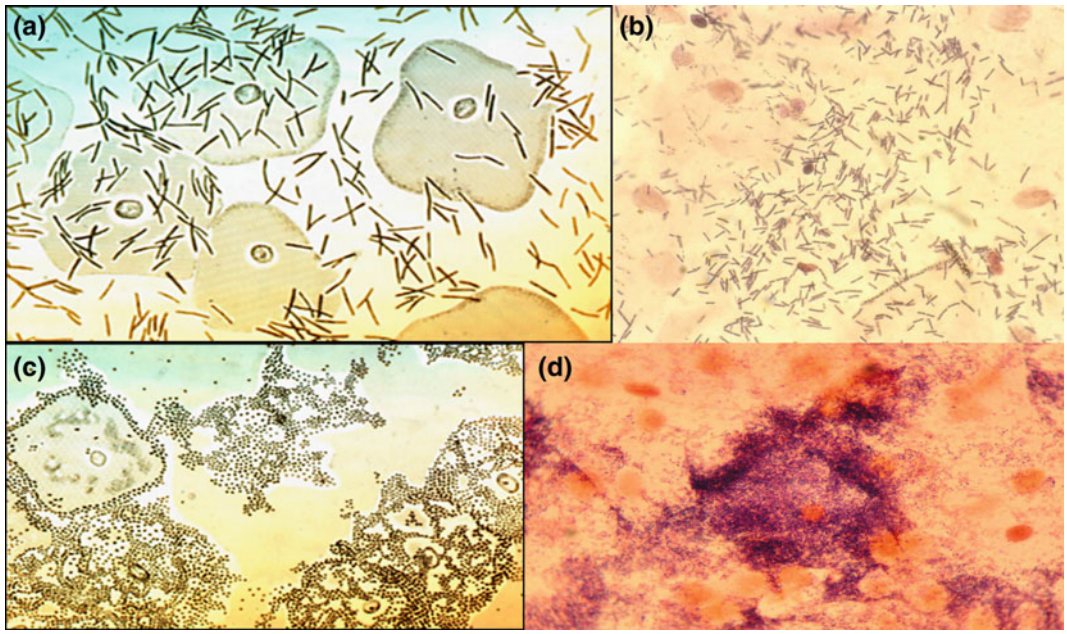

Fig. 9.3 **a** Normal saline wet mount. **b** Normal vaginal gram stain demonstrating squamous epithelial cells and abundant lactobacilli. Parts **a** and **b** courtesy of Phillip Hay. **c** Saline wet mount demonstrating clue cells. **d** Clue cells on vaginal gram stain

been validated or received FDA approval. Such tests usually provide results after 2 or 3 days and results are often confusing to unenlightened practitioners. Overall molecular testing appears reliable, is not inexpensive but may not offer any advantage to practitioners skilled in microscopy.

Another extremely valuable diagnostic modality is Gram stain assessment and determination of the Nugent score [24]. The Nugent score has now emerged as the "gold standard" allowing retrospective validation of BV diagnosis; extremely useful in clinical research studies. Unfortunately Gram stain performance and Nugent score measurement is not and is unlikely to be widely available. Moreover, this method provides no specific microbial identification and is likely to be replaced by molecular techniques that offer greater qualitative and quantitative specificity.

Treatment

Treatment is recommended for women with symptoms. Available oral or vaginal therapies efficiently achieve relief of symptoms and signs and in addition reduce the risk for acquiring *C. trachomatis*, *N. gonorrhoeae*, HIV and other viral STIs [47]. Only two classes of drugs are available: nitroimidazole agents and clindamycin [48, 49]. The recommended regimens as advised by the Centers for Disease Control and Prevention (CDC), were recently updated and are seen in Table 9.2 [50]. A variety of additional alternative regimens including higher dosage metronidazole gels or ovules have been studied but additional data, especially comparative data, are still needed.

Several studies have evaluated the clinical and microbiologic efficacy of using intravaginal lactobacillus formulations or probiotics to treat BV and restore normal flora, but data remain limited and further studies are needed [51, 52].

As mentioned above, in the absence of data supporting the efficacy of treating male sex partners of women with BV, the routine treatment of sex partners is not recommended [15].

Women with RBV constitute a growing number of extremely frustrated women requiring multiple repeated antimicrobial regimens. Recurrence is estimated to occur in 30–40% of

Table 9.2 CDC recommendations for BV Treatment (2015) [50]

Metronidazole 500 mg orally twice a day for 7 days
or
Metronidazole gel 0.75% one full applicator (5 g) intravaginally, daily for 5 days
or
Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for 7 days
Alternative Regimens
Tinidazole 2 g orally once daily for 2 days
or
Tinidazole 1 g orally once daily for 5 days
or
Clindamycin 300 mg orally twice daily for 7 days
or
Clindamycin ovules 100 mg intravaginally once at bedtime for 3 days

women within 3 months of a recommended regimen in an adherent patient and may reach 90% in 9–12 months [53]. Predicting likelihood of recurrence after a treated episode is difficult, although detection of certain BV—associated organisms have been associated with antimicrobial resistance and might determine risk for subsequent treatment failure [21, 22, 54]. Limited data are available regarding optimal management strategies for women with RBV. The initial approach includes switching to a different drug class. Retreatment with the same regimen usually results in short-term relief from symptoms only. Maintenance suppressive regimens with twice weekly vaginal metronidazole gel (0.75%) for 4–6 months has been shown to reduce recurrences, although this benefit might not persist when suppressive therapy is discontinued [55]. Limited data suggests that an initial nitroimidazole regimen followed or accompanied by intravaginal boric acid and finally 4–6 months of maintenance twice weekly 0.75% metronidazole gel appears to be the current method of choice [56]. Boric acid is given to eliminate vaginal biofilm. Monthly oral or high dose vaginal metronidazole (750 mg) is effective in reducing incident BV and promoting colonization with normal flora [57].

Other measures that may potentially decrease risk of RBV include removal of IUDs, use of condoms and oral contraception although confirmatory data is entirely lacking. As mentioned above, and although an attractive option, use of vaginal probiotics has yet to be shown to be effective in women with RBV.

Of note, patients who have BV and are also infected with HIV should receive the same treatment regimen as those who are HIV negative [50]. BV appears to recur with higher frequency in HIV positive women, [58] although reliable comparative data are lacking. In HIV positive women with concurrent infection of BV and trichomoniasis, the presence of BV was associated with early failure of the metronidazole single dose treatment for trichomoniasis and multidose regimens are recommended [59, 60].

In spite of the formidable list of complications that follow both asymptomatic and symptomatic BV and are even apparent in some women with Nugent determined intermediate flora scores, treatment for asymptomatic BV is still not recommended although this premise has been challenged. Little data exists of the benefits on efficacy of the treatment of HIV infected women with asymptomatic BV in spite of its widespread prevalence.

Conclusion

Practitioners responsible for care of women at high risk for or with established HIV infection need to recognize the importance of BV in this population. BV is more common in the HIV infected population and, as with all women regardless of HIV infection, is difficult to cure and even to achieve long term remission. Moreover, BV is associated with a growing number of obstetric and gynecologic complications, primarily the risk of acquiring additional STIs particularly HIV infection. HIV-infected women co-infected with trichomoniasis and BV responds less well to conventional metronidazole therapy for trichomonas. New drugs effective against the

recently identified microorganisms associated with the BV microbiome are urgently needed, as is a better understanding of its pathophysiology.

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Hepatitis B and C

10

Joseph Carlin, Maria Cassia Mendes-Correa and Marina Núñez

Introduction

With the improved survival of HIV-infected patients due to ART, liver disease secondary to viral hepatitis has emerged as an important cause of morbidity and mortality in this population [1–8]. Sexual transmission is the primary route of HBV infection in the western world, and while the main transmission route for HCV is intravenous drug use, over the past 10 years sexual transmission among MSM has been identified as a significant risk for HCV infection in the HIV population [9]. This has implications for screening practices and new approaches are being implemented. In this chapter we will review epidemiology, diagnostic, and clinical aspects, new developments in basic science and a general approach to treatment of HBV and HCV in the setting of HIV coinfection.

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Basic Science Concepts

HBV is a small, enveloped, double-stranded DNA virus, with hepatic tropism that can cause both acute and chronic infection. The virus particle contains a DNA polymerase which has reverse transcriptase activity similar to that of HIV. Because of this similarity, some medications which are part of HIV therapy also have activity against HBV, and this should be considered when planning therapy [9]. A special DNA structure called covalently closed circular DNA (cccDNA) may permanently remain in the nuclei of infected cells, and be responsible for flare ups after apparent resolution of the infection.

HBV is efficiently transmitted through sexual contact with infected individuals [10]. Hepatitis B surface antigen (HBsAg) or HBV DNA has been detected in body fluids and mucosal surfaces including semen, menstrual blood/vaginal discharge, saliva, feces, and the rectal mucosa. In addition, animal models have shown the infectiousness of human semen through intravaginal instillation or inoculation experiments [10]. HIV infection is one of the risk factors associated with HBV infection, and groups at highest risk for HBV sexual exposure include MSM, commercial sex workers, and individuals attending STD

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clinics. The Young Men's Survey, a survey of 3432 MSM aged 15–22 years in US metropolitan areas conducted from 1994 to 1998, found a linear increase in HBV prevalence with age [11]. Therefore, prevention of HBV infection in this group at high risk is of the utmost importance. However, despite the availability of hepatitis B vaccination, immunization among at-risk adults remains low [10–12]. In addition, HIV infection is associated with poor response to HBV vaccination. In a recent report, high serum HIV RNA levels and elevated serum IgG1 and total IgG were associated with poorer response to HBV vaccination among HIV-infected MSM [13]. Finally, coinfection with multiple HBV genotypes and the generation of recombinant forms has been reported among HIV-infected MSM [14]. More studies are needed to determine if these recombinant viruses could affect the pathogenicity of HBV or its response to treatment.

HCV is an enveloped positive-sense RNA virus. Part of the virus' life cycle depends on an error-prone RNA-dependent RNA polymerase, which has made vaccination difficult due to a fast mutation rate and broad genetic variability based on geography. There are seven genotypic types, named with numbers 1–7, with type 1 being the most common genotype in the United States and most of the world [15]. After acute HCV infection, the presence of HIV appears to make spontaneous HCV clearance less likely. This may be related to the diminished number and function of natural killer (NK) cells and the activity of NK-like T cells in HIV-infected patients [16, 17]. Interestingly, the reports of significantly more frequent HCV clearance among MSM in the absence of injection drug use (IDU) (49% in non-IDUs and 23% in IDUs) suggest that the immune mechanisms responsible for a successful response to acute HCV infection leading to spontaneous clearance differ by mode of acquisition [18].

Studies using molecular analysis have confirmed low incidence of HCV heterosexual transmission [10, 19, 20]. However, transmission between male sexual partners has been well documented, primarily among MSM who are infected with HIV [9, 10]. The use of molecular epidemiology has defined HCV transmission clusters within MSM networks, further detailing sexual transmission in this group [10]. Phylogenetic analysis of 226 HCV isolates from HIV-infected MSM with recent HCV infection identified a large international network of HCV transmission among HIV-positive MSM in Europe [21]. Molecular clock analysis indicated that the majority of the transmissions (85%) had occurred since 1996. In this population, reinfection after spontaneous or treatment-related clearance is not infrequent [10, 22]. Through serial sequencing of HCV fragments it has been shown that when a second infection occurs, it is more frequent to acquire a new genotype than to be reinfected with the primary genotype [23].

Case Illustration

A male in his late thirties presented for regular follow-up of HIV infection. He had been diagnosed 13 years earlier, when he had a CD4 of 20 cells/mm^3 and HIV RNA of 2 million copies/mL, and had reported sex with both men and women as HIV-risk factors. Comorbidities at that time included rectal warts. He initiated antiretroviral treatment (ART) soon after his diagnosis. He initially received lamivudine, tenofovir disoproxil fumarate (TDF), and efavirenz, later on co-formulated emtricitabine/TDF plus efavirenz, and thereafter ritonavir-boosted lopinavir, didanosine and co-formulated zidovudine/lamivudine. He was intermittently compliant with the medication until he self-discontinued ART 5 years later. He was lost from follow-up for 1 year, and when he resumed his care, a virtual phenotype revealed reduced TDF activity, and some degree of resistance to all nucleoside reverse transcriptase inhibitors except zidovudine. Based on those results, a ritonavir-boosted darunavir and raltegravir regimen was prescribed, which he had taken for approximately seven years at the time of the clinic visit. Routine laboratory tests revealed elevated alanine aminotransferase (ALT) at 227 and aspartate aminotransferase (AST) levels at 247, up from 35 and 34, respectively, 6 months earlier,

with a bilirubin of 0.8 and an alkaline phosphatase of 87. These results triggered acquisition of hepatitis serologies and hepatitis B surface antigen (HBsAg), and hepatitis B core antibody (anti-HBc) and HBeAg were found to be reactive, with HBV DNA levels of >170,000,000 IU/mL. Repeat laboratory tests 1 week later revealed a decrease in ALT to 155 and in AST to 78. CD4 counts were 920 cells/mm^3 and HIVRNA <20 copies/mL. The patient reported fatigue and a four pound weight loss over the previous few weeks. At a follow-up visit 3 months later he remained clinically stable and ALT and AST were down to 32 and 27, respectively, while HBVDNA levels were unchanged. A retrospective review of his medical records revealed that he had negative anti-HBc at the time of HIV diagnosis, and that he had been vaccinated against hepatitis A and B at that time. No hepatitis B surface antibody (anti-HBs) test was found on record. Of note, the patient did not disclose any recent sexual exposure to a potentially HBV-infected individual. Six months after diagnosis of HBV infection, his HBsAg remained reactive, his transaminases were AST 54 and ALT 52, and HBVDNA remained at >170,000,000 IU/mL. Fixed combination TDF/emtricitabine was added to his ART.

This patient presented initially with acute hepatitis B that evolved to chronic infection, and illustrates several points: (1) HIV-infected patients may not respond adequately to HBV vaccination, remaining at risk for HBV infection; (2) HBV susceptible patients on tenofovir-free ART likely have a higher risk of HBV infection; and (3) MSM are at high risk for HBV infection, and prevention should be emphasized in this group.

Epidemiology

Epidemiology of Hepatitis B Infection

The prevalence of HBV among HIV-infected individuals is higher than in HIV-negative patients, ranging from 8 to 15% with variations according to geography and risk category [2, 9, 24–26]. Prevalence is higher among MSM and in Asian and developing countries [9]. While in nations endemic for HBV, perinatal transmission is most common, in areas of low prevalence, such as the United States, the HBV transmission route is most often sexual. The incidence of HBV infection has been shown to be higher in HIV-infected compared to HIV-uninfected MSM [27]. In that same study, effective ART was associated with lower HBV incidence, but even in the era of highly active ART, the incidence of HBV among MSM remains high. HIV-infected patients exposed to HBV are more likely to progress from acute HBV to chronic HBV [24]. The HIV Outpatient Study (HOPS) examined prevalence of chronic HBV coinfection in HIV-infected patients from 1996 to 2007 at eight outpatient centers across the United States and found a prevalence ranging from 7.8 to 8.6%, without changes over time, and which was roughly 20 times higher than the general population [28]. MSM age 35–44 have the highest prevalence of HBV infection within the HIV population. Furthermore, this study found that while vaccination rates had increased during this 20 year period, it had not reduced the prevalence of HBV coinfection in HIV-infected patients [28]. Along those lines, a study revealed that the risk of HBV infection following HIV diagnosis decreased with higher CD4 counts and use of HBV-active ART, but not with receipt of at least one dose of HBV vaccine [29].

Epidemiology of Hepatitis C Infection

The prevalence of HCV in the HIV population depends on the mode of HIV acquisition, but it is higher than that in the HIV-negative population (<5%) [9, 26, 30–33]. In the United States it has been estimated that 16–33% of HIV-positive patients are coinfected with HCV, and the main route of HCV infection has been IVDU. HCV transmits efficiently through percutaneous blood exposures and has been shown to survive for weeks in syringes [34]. Patients with HIV and intravenous drug use have a prevalence of coinfection greater than 50%. Transmission through contaminated blood products is now rare. Other

factors that have been associated with HCV infection include intranasal cocaine use and tattoo placement [9].

Although heterosexual transmission of HCV is uncommon, it is more likely to occur when the source is HIV–HCV-coinfected [35, 36]. However, in HIV-infected MSM, multiple outbreaks of acute HCV infection have been reported, demonstrating that sexual transmission is an important route HCV infection in this population [21, 36–39]. These outbreaks have coincided with an increase in high-risk sexual behaviors following the introduction of ART, and identified risk factors include unprotected receptive anal intercourse, use of sex toys, non-injection recreational drug use, and concurrent sexually transmitted diseases [21, 36, 37, 39–41]. Patients with HIV infection also have a higher rate of reinfection with HCV, estimated at over 20% within 5 years, which is more than double the rate of reinfection in HIV-uninfected subjects [42]. The incidence of mother-to-child HCV transmission is low, but increases when mothers are HIV-coinfected [27, 43].

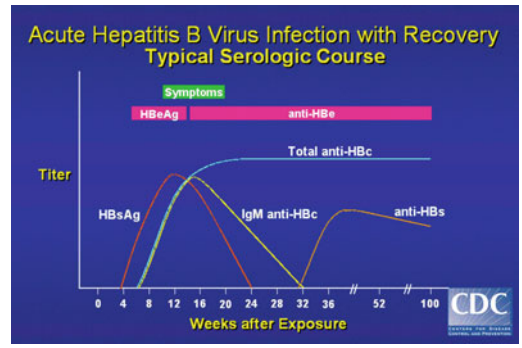

Fig. 10.1 Acute hepatitis B serologic course

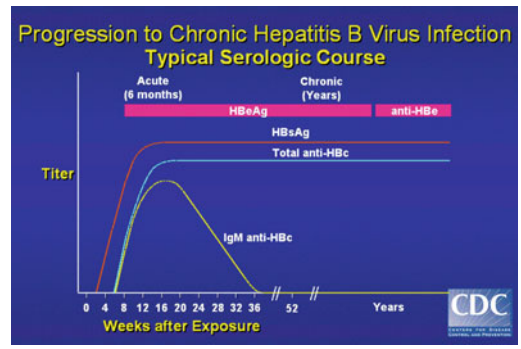

Fig. 10.2 Chronic hepatitis B serologic course

Clinical Presentation

Hepatitis B Infection

After exposure to HBV, there is an incubation period of 45–160 days, 120 days on average. Manifestations during the acute phase range from subclinical to icteric hepatitis and, in some cases, fulminant hepatitis. Acute hepatitis is a clinical syndrome consisting of an influenza-like illness with malaise, fatigue, anorexia, nausea, vomiting, and right upper quadrant discomfort. Often symptoms are ascribed to a routine viral infection and patients may not present for medical attention. Physical signs include jaundice and tender hepatomegaly. The symptoms and jaundice generally resolve after 1–3 months. Figures 10.1 and 10.2 demonstrate the clinical and laboratory course of acute hepatitis B compared with that of chronic hepatitis B [44]. As MSM are at high risk for acute hepatitis B infection, this diagnosis should be considered when addressing liver enzyme elevations in this group.

Some patients do not eliminate the HBsAg after acute infection, and it evolves to a chronic phase, which usually is asymptomatic. Chronic hepatitis B is usually diagnosed coincidentally while performing routine screening. In some patients with chronic HBV, liver disease progresses to cirrhosis. Cirrhotic patients may complain of fatigue, easy bruising, and lower extremity swelling. Ascites, scleral icterus or jaundice, and spider angiomata are findings of advanced cirrhosis. GI bleeding secondary to esophageal varices can occur as a complication of portal hypertension. HBV is a risk factor for the development of hepatocellular carcinoma (HCC), even in the absence of cirrhosis. Patients with HCC can be asymptomatic or present with fatigue, weight loss, or abdominal pain.

Hepatitis C Infection

After exposure to HCV, there is an incubation period of 14–180 days, 45 days on average. Acute hepatitis C often is asymptomatic, although a minority of patients experiences the clinical syndrome of acute hepatitis as described above [9]. The diagnosis of acute HCV infection in asymptomatic patients is often made during workup for new onset liver enzyme elevations. The presence of *IL28B* CC genotype, female sex, and the presence of jaundice at the time of acute HCV infection are associated with subsequent spontaneous HCV clearance, while HIV may have a negative impact. A percentage of patients, depending on the factors above, develop chronic infection, which usually remains asymptomatic for years. In some patients, liver disease progresses to cirrhosis, and at that time other symptoms can occur as described above, and HCC may develop. The risk for liver disease progression for an individual is highly variable. Although liver fibrosis progression is usually slow, rapid fibrosis progression soon after acute HCV infection has been recently reported in predominantly male cohorts that included MSM and drug users [45, 46]. Risk factors for development of significant liver disease include older age at the time of infection, male sex, obesity, and concomitant alcohol use [9]. HIV exerts a negative effect over HCV-related liver disease. Thus, in a meta-analysis of studies performed in the pre-HAART era, HIV coinfection was associated with twofold increased risk of cirrhosis compared to HCV monoinfection [47]. In a like manner, the risk of HCC is higher among HIV–HCV-coinfected compared to non-HIV–HCV-infected patients [48].

Diagnostic Considerations

Hepatitis B Diagnosis

The meaning of HBV serologic markers is outlined in Table 10.1. Additional charts are available at the Center for Diseases Control and Prevention website [44] that can help with the interpretation of specific serologic profiles. A reactive HBsAg indicates infection, either acute or chronic [49]. IGM hepatitis B core antibody (IGM anti-HBc) is always reactive in acute hepatitis B, while total anti-HBc indicates current or past infection, although as an isolated marker could also represent a false positive. ALT and AST levels rise in acute hepatitis B, typically up to 1000–2000 IU/L. HBsAg persistence after 6 months defines chronic hepatitis B infection.

All HIV-positive patients should be screened for HBV (HBsAg) at their initial evaluation. Besides being an opportunity to detect an infection which is more prevalent in the HIV population, the HBV status has implications for HIV treatment [9]. HBsAg negative patients should be also tested for anti-HBs, and if negative, they should receive HBV vaccination series. Patients found to have reactive HBsAg in the absence of findings suggesting acute hepatitis is considered

Table 10.1 Significance of specific HBV serological tests

HBV serological test	Significance
HBsAg	First marker to appear after infection Defines current infection (chronic if >6 months)
Anti-HBcAb (total)	Indicates present or past infection
Anti-HBcAb IGM	Indicates acute HBV infection
HBeAg	Indicates active viral replication
Anti-HBeAb	Appears after HBeAg clearance and indicates reduced or absent viral replication
Anti-HBsAb	Indicates immunity to HBV, acquired either after recovery from acute infection or after vaccination

to have chronic HBV, although HBsAg can be transiently positive after receiving HBV vaccination [50]. In patients with chronic HBV, hepatitis B e-antigen (HBeAg) and quantitative HBV DNA should be obtained. A reactive HBeAg indicates high viral replication and this has implications for treatment response. HBeAg clearance is one of the treatment endpoints in HBeAg-positive chronic HBV. Hepatitis delta virus (HDV) serology is indicated in intravenous drug users and in individuals originating from the Mediterranean area or some parts of South America [51].

Assessment of the liver status is also indicated in patients with chronic HBV. Transaminase levels in general reflect inflammation of the liver, while albumin and coagulation indicate liver synthesis function. Of note, the upper limit of normal for transaminases is considered 30 IU/L for males and 19 IU/L for females [52]. Abdominal ultrasound can detect signs of cirrhosis and portal hypertension and it is at the same time the method of choice for HCC surveillance which is indicated in certain groups, even in the absence of cirrhosis [9, 51, 52]. Given HBV's oncogenic properties, HIV providers should make efforts to adhere to hepatocellular carcinoma screening in HIV–HBV-coinfected patients as recently highlighted by a retrospective study [9, 52, 53].

Hepatitis C Diagnosis

After HIV diagnosis, all patients should have routine HCV screening using the most sensitive immunoassays licensed for detection of anti-HCV antibody [9]. Third-generation HCV EIA assays allow anti-HCV detection nearly 4–6 weeks after infection with sensitivities and specificities over 99% [49]. In those with positive anti-HCV antibody, serum HCV RNA should be obtained for confirmation since a proportion of patients with positive anti-HCV antibody have spontaneously cleared the infection [54]. Once the diagnosis has been confirmed, there is no benefit to serially testing HCV RNA load in a patient proven to have chronic HCV infection. However, HCV RNA testing may be considered in an HIV patient with significant risk factors for HCV who is negative for anti-HCV as, although rare, false-negative anti-HCV antibody results are possible, especially in patients with advanced HIV disease [9]. In patients found to be chronically infected with HCV, assessment of liver disease is also indicated as described above, with an emphasis in liver fibrosis staging. HCC surveillance with liver ultrasound every 6 months is indicated in HCV-infected patients with cirrhosis.

Anti-HCV antibody-negative patients at risk for HCV infection, including sexually active MSM, are recommended to continue annual screening with HCV antibody testing [9]. Anti-HCV antibody testing can be negative in the first phase of an acute infection. Therefore, in HIV patients with high-risk behaviors, negative anti-HCV and symptoms consistent with acute HCV infection or unexplained elevated liver transaminases, testing of HCV RNA should be performed [9, 10]. In a recent study, acute HCV infections were diagnosed in the absence of significant aminotransferase elevations, and therefore HCV testing should not only be triggered by elevated transaminase levels [55, 56]. Interestingly, in a study performed in MSM, HCV antibody seroreversion (anti-HCV clearance) occurred in almost one-third of patients [22].

Treatment

Hepatitis B Infection

Before addressing the treatment approach to HBV, the importance of HBV prevention, which involves avoiding exposures and HBV vaccination, should be highlighted. All HIV-infected patients without chronic HBV (negative HBsAg) and without proven immunity to HBV (negative anti-HBsAb) should be vaccinated with HBV vaccine [9]. This is of special importance in patients with high-risk behaviors associated with HBV infection and on ART not containing HBV-active drugs. Given decreased vaccine responses among HIV-infected patients,

anti-HBs titers should be obtained 1 month after completion of the vaccine series, and for patients with anti-HBs levels <10 IU/mL, a second vaccination series is recommended [9]. HIV-infected patients have decreased response to HBV vaccine, and different strategies to improve response have been proposed [57]. For patients with isolated anti-HBc, a recent prospective study supports vaccination with one dose of recombinant HBV vaccine, and for those with anti-HBs <10 m IU/mL 4 weeks after the initial vaccine, vaccination with three additional double doses [58]. Including tenofovir in the ART among those patients with no evidence of HBV immunity and at high risk for STIs, especially MSM, should be considered.

In the presence of HIV, coordination of HBV and HIV therapies is needed [9]. Tenofovir, entecavir, lamivudine, emtricitabine, and telbivudine have activity against HIV and should not be used in the absence of ART because of the likely development of HIV-resistance mutations. Hepatic flares due to immune reconstitution, especially in the absence of anti-HBV-active drugs, have been reported [9]. Among patients who eventually eliminate the HBsAg, reverse seroconversion may occur where HBsAg becomes reactive again, accompanied by transaminitis. There is also a higher risk of selection of lamivudine resistance and worse response to interferon in HIV–HBV-coinfected compared to non-HIV-infected subjects [59]. Some data suggest an association between higher CD4 counts and achievement of HBV suppression and HBeAg and HBsAg clearance [60–63].

The indications for HBV treatment are summarized in Fig. 10.3. However, regardless of CD4 cell count or need for HBV treatment, ART that includes agents with activity against both HIV and HBV is recommended for all patients coinfected with HIV and HBV [9]. Because both tenofovir and emtricitabine have anti-HBV activity, this is the nucleos(t)ide backbone of choice as part of ART for HIV–HBV-coinfected patients. Tenofovir, the most important piece in the treatment of HBV, is active against wild-type and lamivudine-resistant HBV strains [9, 64]. Treatment with HBV-active therapy should be continued indefinitely. In one study, discontinuation of HBV-active ART was noted to be followed by an HBV flair in 30% of studied patients [65]. Studies show that virological HBV outcomes in treated HIV–HBV-coinfected subjects are more favorable when tenofovir is included [57, 60, 61, 64–70]. A recent study reported HBeAg clearance in 46% after a median of 3 years, and HBsAg clearance in 7.4% after a median of 4.6 years [71]. Predictors of undetectable HBV DNA on treatment include negative HBeAg status, higher CD4 counts and lower HBV DNA levels at baseline, greater CD4 recovery while on HAART, longer HBV treatment duration, and older age [57, 60, 64, 66, 67, 71]. HBV DNA suppression may take years and increases over time while on tenofovir (>90% after 5–7 years of treatment reported), but some

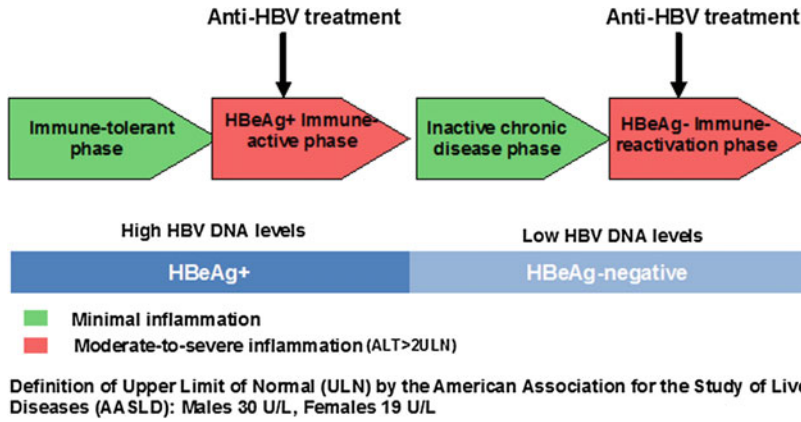

Fig. 10.3 Indications for HBV treatment

HBeAg-positive patients do not achieve full control of HBV replication even after prolonged tenofovir use [68, 71]. One explanation for an incomplete response to tenofovir is poor adherence, as HBV requires more rigorous adherence to oral therapy than HIV, although there may be other causes [70]. In an adherent patient with a partial virologic response to tenofovir, the drug should be continued with monitoring of HBV DNA levels. Improvement of response with the addition of entecavir has been reported, but whether such "intensification therapy" is required is unclear [9]. As TDF has the potential to cause renal impairment, in order to avoid TDF in patients with renal dysfunction, entecavir can be added to the ART regimen. However, virological outcome data after such a switch are lacking [66]. In persons with known or suspected 3TC-resistant HBV, close monitoring is recommended since entecavir resistance may emerge more quickly in this setting. Recently, tenofovir alafenamide (TAF) has been approved for the treatment of HIV [72]. TAF is associated with fewer bone and kidney abnormalities, but data are very limited at this time regarding clinical use against HBV.

HBV-active ART has been shown to ameliorate the development of hepatic fibrosis and to reduce liver-related mortality in HIV/HBV-coinfected individuals treated with ART containing HBV-active drugs [73, 74]. However, despite available treatment, mortality remains high for the HIV–HBV-coinfected population [63]. While treatment with HBV-related ART prevents liver decompensation, it does not protect as much against the development of hepatocellular carcinoma, which remains a significant cause of death in this population.

Hepatitis C Infection

Interferon-free direct-acting antiviral (DAA) combinations have revolutionized the treatment of HCV. In the interferon era, the HIV–HCV-coinfected was a special population characterized by poor response to HCV treatment. DAAs, contrary to interferon-based treatments, are well tolerated and achieve cure rates of above 90% [76]. Limited data on HCV Rx with DAAs in HIV–HCV-coinfected subjects suggest that they respond as well as non-HIV patients [75, 76]. Current guidelines recommend applying general HCV treatment recommendations to the treatment of patients with HIV coinfection, although with some special considerations [9, 76]. The treatment options available for the treatment of HCV according to genotype are summarized in Table 10.2.

HCV treatment in HIV-coinfected patients requires attention to drug-to-drug interactions that can occur between DAAs and antiretroviral medications [76]. Drug interactions between DAAs and antiretroviral drugs are summarized in Table 10.3. Daclatasvir requires a decrease in the dose to 30 mg daily with ritonavir-boosted atazanavir and an increase to 90 mg daily with efavirenz or etravirine. Ledipasvir increases tenofovir levels, which may increase the risk of tenofovir-associated renal toxicity. Therefore, the use of ledipasvir/sofosbuvir fixed-dose combination along with TDF should be avoided in those with CrCl below 60 mL/min. In a like manner, ledipasvir/sofosbuvir fixed-dose is not recommended in combination with TDF and ritonavir-boosted HIV protease inhibitors or cobicistat because the tenofovir levels could exceed those deemed renally safe. Simeprevir should not be used with cobicistat, efavirenz, etravirine, nevirapine, or any HIV protease inhibitor. Paritaprevir/ritonavir/ombitasvir/dasabuvir combination has multiple drug-to-drug interactions and should be used with antiretroviral drugs with which they do not have substantial interactions such as atazanavir (although the dose of ritonavir used for boosting should be held), dolutegravir, emtricitabine, enfuvirtide, lamivudine, raltegravir, and tenofovir. Protease inhibitors are not recommended to be used along with the fixed combination elbasvir/grazoprevir because they may increase the risk of ALT elevations due to an increase in grazoprevir plasma concentrations. The use of elbasvir/grazoprevir with efavirenz is contraindicated because efavirenz causes significant decreases in elbasvir and grazoprevir plasma concentrations.

Table 10.2 HCV treatment recommendations by genotype

Regimen	Genotype/subtype					
	1a	1b	2	3	4	5 and 6
Sofosbuvir/Ledipaspir (Harvoni®)	8–12 weeks no cirrhosis 12–24 weeks cirrhosis				12 weeks	12 weeks
Sofosbuvir/Ledipaspir (Harvoni®) + ribavirin	12 weeks cirrhosis and prior treatment failure					
Paritaprevir/r/Dasabuvir/Ombitasvir (Viekira pak™)		12 weeks no cirrhosis				
Paritaprevir/r/Dasabuvir/Ombitasvir (Viekira pak™) +ribavirin	12 weeks no cirrhosis 24 weeks cirrhosis	12 weeks cirrhosis			12 weeks (Paritaprevir/r/Ombitasvir, Technivie™)	
Sofosbuvir + ribavirin			12 weeks no cirrhosis 16 weeks cirrhosis			
Simeprevir + sofosbuvir	12 weeks no cirrhosis 24 weeks cirrhosis					
Simeprevir + sofosbuvir +ribavirin	24 weeks cirrhosis					
Daclatasvir + sofosbuvir	12 weeks no cirrhosis 24 weeks cirrhosis		12 weeks	12 weeks no cirrhosis 24 weeks cirrhosis		
Daclatasvir + sofosbuvir + ribavirin	24 weeks cirrhosis			24 weeks cirrhosis		
Sofosbuvir + PegInterferon + ribavirin				12 weeks		12 weeks
Elbasvir/grazoprevir (Zepatier™)	12 weeks no baseline NS5A polymorphisms	12 weeks			12 weeks treatment naive	
Elbasvir/grazoprevir (Zepatier™) + ribavirin	16 weeks baseline NS5A polymorphisms	12 weeks protease inhibitor experienced			16 weeks treatment-experienced	

Table 10.3 Recommendations related to drug interactions between DAAs and antiretroviral drugs

HCV drug(s)	Adjustment required	Not recommended
Daclatasvir	Ritonavir-boosted atazanavir: ↓ dose to 30 mg/day Efavirenz or etravirine: ↑ dose to 90 mg/day	
Simeprevir		Cobicistat, efavirenz, etravirine, nevirapine, HIV protease inhibitors
Sofosbuvir		Tipranavir
Ledipaspir/Sofosbuvir (Harvoni®)		Tenofovir disoproxil fumarate with CrCl <60 mL/min Tenofovir disoproxil fumarate with cobicistat Ritonavir-boosted HIV protease inhibitors
Paritaprevir/r/Dasabuvir/Ombitasvir (Viekira pak™)	Ritonavir used for boosting of HIV protease inhibitors should be held HIV protease inhibitor should be administered at the same time as the HCV drugs	Without antiretroviral therapy With darunavir, ritonavir-boosted lopinavir, efavirenz, or rilpivirine
Elbasvir/grazoprevir (Zepatier™)		Efavirenz Protease inhibitors (atazanavir, darunavir, lopinavir, saquinavir, tipranavir)
Ribavirin		Didanosine, stavudine or zidovudine

Several trials specifically included HIV–HCV-coinfected patients. In the ERADICATE study, 50 HIV/HCV-coinfected, HCV genotype 1 patients without cirrhosis were treated with ledipasvir/sofosbuvir [77]. Overall, 98% achieved sustained virologic response at 12 weeks (SVR12). A larger study, ION-4, reported similar outcomes with ledipasvir/sofosbuvir [78]. In this study a total of 335 HIV/HCV-coinfected patients (genotypes 1 and 4), 55% HCV treatment-experienced, and 20% with cirrhosis received ledipasvir/sofosbuvir once daily for 12 weeks. Overall, the SVR12 rate was 96% (321/335). There are limited data regarding the efficacy of an 8-week duration course of ledipasvir/sofosbuvir in HIV/HCV-coinfected patients. Paritaprevir/ritonavir/Dasabuvir/Ombitasvir (PrOD) fixed combination was studied in 63 HIV/HCV-coinfected patients in the TURQUOISE-1 study. A small proportion of patients had cirrhosis. Patients were randomized to receive either 12 weeks or 24 weeks of PrOD and weight-based ribavirin (RBV). Twelve patients had cirrhosis, and the majority had HCV genotype 1a. SVR was 93.5% for the arm receiving 12 weeks of PrOD and RBV, and 90.6% for the 24-week arm [79]. The PHOTON studies included HIV/HCV-coinfected patients with HCV genotypes 2 ($n = 45$ treatment naïve and $n = 30$ treatment-experienced) and 3 ($n = 99$ treatment naïve and $n = 66$ treatment-experienced) and evaluated sofosbuvir and weight-based RBV. Treatment-naive patients received 12 weeks of treatment if they had genotype 2, and 12 or 24 weeks if they had genotype 3. All treatment-experienced patients were treated for 24 weeks. Patients with compensated cirrhosis (15%) were included. SVR12 rates among treatment naive were 92% for genotype 2 and 67% for genotype 3. Among treatment-experienced, SVR12 rates were 92% for genotype 2 and 88% for genotype 3. Among patients infected with genotype 3, 24 weeks duration resulted in higher SVR (92%) than 12 weeks (67%) [80]. ALLY-2

evaluated 12-week treatment with daclatasvir and sofosbuvir once daily in patients with HIV/HCV coinfection and HCV genotypes 1–4 treatment-naive ($n = 151$) and treatment-experienced ($n = 52$), including 14% with cirrhosis [81]. SVR12 was 97% across genotypes, 97% among treatment-naive, and 98% among treatment-experienced patients. Elbasvir and grazoprevir have been studied in HCV genotype 1 HIV/HCV-coinfected patients in the C-EDGE study. Among 189 treatment naïve HCV genotype 1-infected patients, 95% achieved SVR after 12 weeks of treatment with elbasvir/grazoprevir. Among 96 treatment-experienced patients, SVR was achieved in 94% after 12 weeks of treatment with elbasvir/grazoprevir (90% subtype 1a and 100% subtype 1b) and in 97% after 16 weeks of treatment with elbasvir/grazoprevir and RBV (95% subtype 1a and 100% subtype 1b) [82, 83].

Few HIV/HCV-coinfected patients with cirrhosis have been included in clinical trials of DAAs, and no data are available for patients with HIV coinfection, renal insufficiency, post-solid organ transplantation, or with prior failure to DAAs. Despite a lack of data, when treatment is necessary, general guidelines for HCV-infected individuals are recommended, with consideration of drug interactions [76]. Finally, HBV reactivation in anti-HBc-positive patients with or without HBsAg can occur during treatment for HCV with DAAs [84–86]. The immune mechanisms leading to HBV reactivation with DAAs as well as the optimal management are unclear at this time. Regarding treatment of acute HCV infection, initially there was enthusiasm to identify acute infection and rapidly initiate treatment when the efficacy of the treatment of acute HCV infection was superior to the treatment of chronic infection, especially for genotype 1 [76]. However, the efficacy of current treatments for chronic HCV infection possibly eliminates the advantage of early treatment. Therefore, monitoring for spontaneous clearance for a minimum of 6 months is recommended in this setting. Nevertheless, for some persons, there may be additional benefits of early treatment, such as prevention of severe complications or of transmission to others. If for those reasons a decision is been made to initiate treatment during the acute infection period, the same regimens used for chronic HCV infection are recommended [76].

Conclusion

Due to shared routes of viral transmission, coinfection with HIV and HCV and/or HBV is not uncommon. Screening for these infections at initial evaluation and during follow-up is an important aspect of HIV care, as chronic viral hepatitis carries significant morbidity and mortality over time, and as acute infection continues to fuel the epidemics of viral hepatitis, especially among MSM. HIV alters the course of HCV and HBV infections in several ways, and the interactions between ART and the treatments for HCV and HBV pose unique challenges to the management in HIV-coinfected patients. Significant progress has been made in the treatment of HBV and HCV, resulting in improved outcomes.

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Part III
Special Populations

Sexually Transmitted Infections in Men Who Have Sex with Men

11

Nicholas Van Wagoner and Kenneth H. Mayer

Introduction

The term "men who have sex with men" (MSM) describes a heterogeneous group of men with diverse sexual behaviors, identities, and healthcare needs, but who are at risk for specific STI because of specific practices [1]. MSM is a behavioral term, and as such may include men who are married to women, who do not identify as male, as well as men who identify as "gay." Hence, it is incumbent for clinicians to ask about sexual behaviors in a nonjudgmental way, since a patient's appearance or marital status may not be informative regarding specific STI risks. MSM often have higher rates of STI and HIV than demographically matched heterosexual men [2]. The reasons for these higher STI and HIV rates involve multiple intersecting variables (Fig. 11.1). This chapter will focus on (1) the biological and behavioral factors relevant to STI in MSM, (2) the STI epidemiology in MSM, (3) pertinent clinical issues unique to MSM, including the extragenital manifestations of STI, (4) current screening and diagnostic recommendations, and (5) treatment considerations.

Case 1

A 32-year-old male presents with an ulcer on the roof of his mouth. He first noticed it one day prior to presentation. He denies trauma to the area. The lesion is not painful. He has no history of such lesions in the past and denies a history of cold sores. He has no other physical complaints. He has sex with men, identifies as gay, and has had receptive oral sex with four casual partners in the last 3 months. He does not use condoms for oral sex. He was screened for STI 6 months ago at which time a serologic rapid plasma reagin (RPR) test was nonreactive. His urethral and rectal screening tests were negative for gonorrhea and chlamydia but oropharyngeal screening was positive for gonorrhea. He was appropriately treated with eradication of oropharyngeal gonorrhea noted at retesting 3 months later. Today, on examination, there is a clean-based ulcer with erythematous heaped borders on the hard palate (Fig. 11.2). Palpation of the lesion produces no pain or bleeding. The rest of the physical examination, including the skin and anogenital examinations, are normal. Based on these findings, the healthcare provider makes a clinical diagnosis of primary syphilis with an oral chancre and treats the patient with Benzathine penicillin G 2.4 million units intramuscularly in a single dose. An RPR is performed in the clinic's

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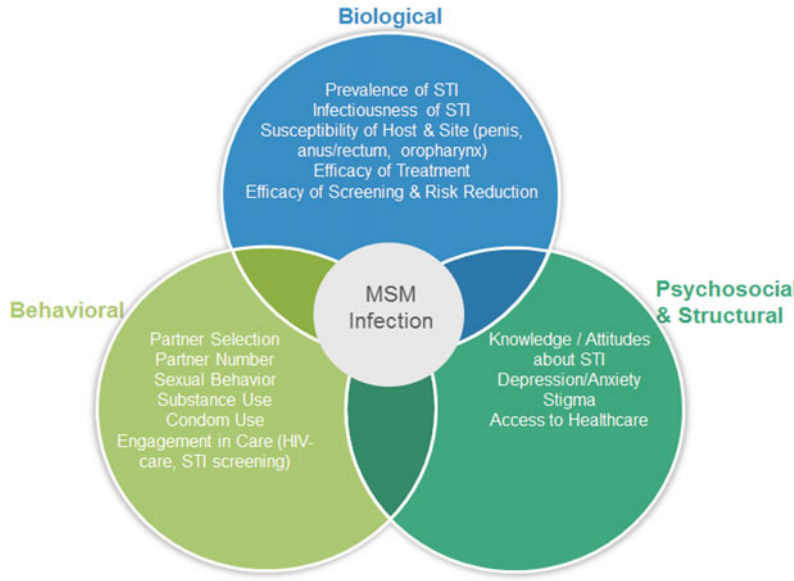

Fig. 11.1 Factors influencing STI transmission and acquisition among MSM

lab and is reactive (1:16). The *Treponema pallidum* passive particle agglutination (TP-PA) assay is sent for confirmation and is positive.

- The chancre of Primary Syphilis is seen at the site of inoculation and is often extragenital.
- When primary syphilis is suspected, providers should empirically treat at the time of presentation and prior to serologic confirmation.

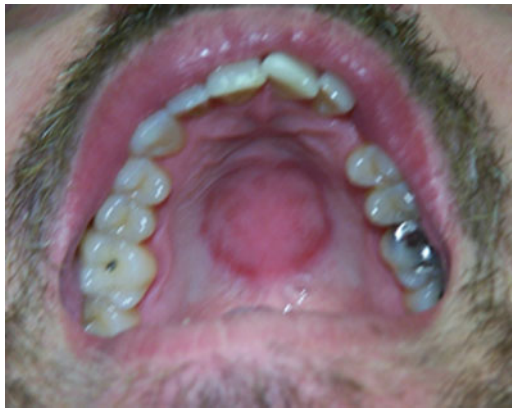

Fig. 11.2 Oral chancre of primary syphilis. Courtesy of Jeffery D. Hill, DMD

Case 2

A 23-year-old male presents for evaluation of left lower quadrant abdominal pain and rectal bleeding for the past 3 weeks. At symptom onset, he reported watery diarrhea and headache. These symptoms were followed by constant left lower quadrant pain, bloating, and intermittent cramping as well as mucoid discharge, tenesmus, and rectal bleeding that occurred with and in between bowel movements. The patient is HIV-infected on antiretroviral therapy (ART) with an undetectable HIV viral load and a CD4+ T cell count of 751 cells/μl. He has no other medical problems and specifically denies previous episodes of similar symptoms. He reports sex with men and identifies as gay. He engages in oral sex and receptive and insertive anal sex. He reports six partners in the 4 weeks preceding the start of symptoms. He has not had sex since symptoms developed. On examination, no hemorrhoids, fissures, or other perianal lesions are seen. Digital rectal examination is painful but the anal canal is smooth and the prostate is normal size and nontender. Anoscopy reveals a pink, mucoid discharge. The mucosa is friable and bleeds easily when collecting swab specimens. Polymorphonuclear leukocytes are seen on the

gram-stained smear of the exudate but no intracellular diplococci are observed. The patient is diagnosed with proctocolitis with high suspicion for Lymphogranuloma Venereum (LGV). He is prescribed doxycycline 100 mg twice a day for 21 days. Molecular testing is positive for *Chlamydia trachomatis* and negative for *Neisseria gonorrhoeae*, herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2). In follow up at the end of therapy, the patient reports resolution of symptoms. The patient was rescreened for STI 3 months later, per CDC guidelines, and was negative.

- Sexually transmitted proctitis should be considered in MSM with anorectal symptoms.
- Empiric treatment for sexually transmitted causes of proctitis and/or proctocolitis should be considered while awaiting confirmation.
- Proctitis suspected or confirmed to be secondary to LGV requires longer duration (3 weeks) of therapy compared to other chlamydia infections.

Biological and Behavioral Factors Relevant to STI Infection in MSM

There is wide variation in sexual behaviors among MSM, and not all MSM are equally at risk for acquiring STI. However, in general, population-based surveys suggest that MSM have more sexual partners and higher rates of partner concurrency than demographically matched peers, placing them at greater risk for acquiring and transmitting STI [3]. The specific sexual practices reported by MSM are diverse, with oral sex and digital-manual stimulation of the partner's penis and anus being most common [4]. Most MSM also report experience with anal intercourse at some point during their lives [5]. Because the oropharynx and rectum are both susceptible to STI, extragenital infection is common [6, 7]. Further, STI transmission from the oropharynx and rectum to the urethra of the sex partner is well documented and confirmed by the high rates of genital infection among MSM who report only engaging in oral and/or anal insertive sex [7–10]. Oral stimulation of the anus with the tongue (i.e., rimming) is also frequently reported by MSM and has been implicated in the transmission of bacterial STI as well as enteric pathogens, including intestinal parasites, to the partner who provides the oral stimulation [10, 11]. Cytomegalovirus, Hepatitis B, and Human Herpes Virus 8 are found in saliva. Because some MSM use saliva for lubrication during digital stimulation of the anus and anal sex, these viral pathogens can be transmitted to the receptive partner, irrespective of condom use [12]. Use of saliva as a lubricant has also been suggested as an important risk factor for the transmission of gonorrhoeae [13]. Insertion of the hand into the rectum (fisting) has been reported by some MSM. Fisting carries a risk for traumatic bowel injury and has been associated with acute hepatitis C infection [14, 15]. Sex toy use (i.e., dildo, butt plug, fleshlights) can also cause mucosal trauma and act as fomites when sex toys are shared by sex partners [16]. Other sexual practices can place some MSM at risk for STI or trauma that can result in symptoms commonly associated with STI and easily confused with STI syndromes. As examples, urethral sounding is the practice of inserting an object or liquid into the urethra and is associated with urethral irritation, bleeding, and dysuria [17, 18]. Sex play (wax play, cock and ball torture, erotic electrostimulation, etc.) may lead to skin injury and ulceration with lesions mimicking those observed in genital herpes and primary/secondary syphilis.

Behaviors affecting STI risk extend beyond specific sexual practices and partner number. Rectal product use before, during or after anal sex may make the rectal mucosa more susceptible to STI and HIV. Precoital rectal douching, a popular practice among MSM, is linked to greater rates of STI and HIV [19–23]. Hyperosmolar lubricants used during anal sex may cause short term denudation of the rectal mucosa increasing susceptibility to STI and HIV [24, 25]. Postcoital douching is also commonly performed by some MSM [19]. Its relationship to STI is less well understood. Overall, condom use among MSM is declining [26]. Serosorting, the practice

of engaging in condomless sex with only men with the same HIV status, in order to decrease HIV transmission, is well documented among MSM, but has been associated with increased STI transmission [27]. As discussed below, pharmacologic advancements preventing HIV transmission also contribute to the rise in condomless sex among HIV-infected and HIV-uninfected MSM, but these factors do not fully explain recent changes in sexual behaviors among MSM [26].

Because MSM behaviors have been stigmatized by many societies, MSM may internalize societal rejection, and become depressed or anxious [28, 29]. Studies have linked high rates of depression and other behavioral health concerns with condomless sex and other adverse health outcomes, including substance use, as well as avoidance of medical care in anticipation of receiving culturally insensitive care, and/or disclosure of their homosexual behaviors to peers and/or family members [1, 30, 31]. For these reasons, knowledge of a patient's sexual behavior and substance use with focused interventions in these areas may have limited efficacy without understanding and addressing the root cause(s).

The use of recreational drugs and alcohol is common among some MSM and clearly linked to behavioral disinhibition, condomless sex, and higher STI risk [1, 32, 33]. Chemsex, is a specific term for recreational drug use that usually involves drugs that have euphoric or relaxing effects (e.g., gamma-hydroxybutyrate, methamphetamine, and mephedrone) and that alone or in combination prolong sexual sessions [34]. Dangerous in their own right, their use has been linked to STI in MSM [35]. FDA approved drugs for the treatment of erectile dysfunction are also used recreationally alone or in combination with other drugs by some MSM and are also linked to condomless sex and risk for STI and HIV [36]. Although not linked to STI, substance use among MSM extends to tobacco products with adolescent as well adults more likely to smoke tobacco than their heterosexual peers [37, 38].

Technological advancements including internet-based and geospatial sexual partner identification applications are commonly used by some MSM to identify potential sexual partners. Studies suggest that use of these platforms is linked to reporting a greater numbers of casual or unknown sex partners, condomless sex and higher rates of STI [39–41]. Further, the development of highly effective pharmacologic strategies that reduce HIV transmission and acquisition including HIV treatment as prevention and pre-exposure prophylaxis (PrEP) have been associated with higher rates of bacterial STIs and may increase STI through risk compensation (i.e., MSM feeling less concerned about HIV transmission or acquisition) [42–49].

As outlined above, sexual practices are diverse among MSM and may vary over time. Thus, the sexual history should frequently be revisited for screening purposes and discussed with MSM who present with genitourinary, gastrointestinal, or oropharyngeal symptoms. Some MSM may feel uncomfortable discussing their sexual behavior and/or recreational drug use with healthcare providers [50, 51]. Effective sexual history taking requires not only knowledge of sexual practices common to MSM but also the ability to discuss these sexual practices in a respectful way that engenders trust and ensures confidentiality.

Clinical STI Manifestations in MSM

For MSM, the primary sites of sexual exposure include the oropharynx, genitalia, anus, and rectum. When symptoms develop from infection, these are the sites usually involved, with some notable exceptions. Clinical manifestations of STI can vary depending upon HIV status and level of immune compromise.

Urogenital

Genital symptoms are not typically different in MSM and MSW and can be categorized broadly as urethral, ulcerative, and papular. As covered in greater detail elsewhere, symptoms of urethritis include dysuria, urethral itching, and urethral discharge and, in MSM, are most commonly

caused by *N. gonorrhoeae*, *C. trachomatis*, *Mycoplasma genitalium*, and other agents, which have not been fully characterized. Although there is substantial overlap, some studies suggest that the spectrum of organisms responsible for urethritis in MSM may differ from those causing urethritis in men who have sex with women (MSW) and, in MSM, may be transmitted through relatively low risk sexual practices including oral-genital sex although the specific pathogens are poorly understood [52, 53]. Enteric pathogens have also been implicated as a rare cause of urethritis in men who practice insertive anal sex. Less common causes of urethritis include HSV-1, HSV-2, and adenovirus [54, 55]. *Neisseria meningitidis* can also cause urethritis (and rarely proctitis) [56, 57]. *N. meningitidis* colonizes the nasopharynx and urethral transmission can occur through oral sex. Although reports to date do not place MSM at higher risk of *N. meningitidis* urethritis than MSW, colonization rates in oropharynx of MSM are reportedly higher than in other groups and healthcare providers should consider it a potential sexually transmitted pathogen in MSM [58]. In addition, MSM have a substantially higher risk for invasive and often life-threatening disease caused by *N. meningitidis* [59]. Vaccination against the serogroups A, C, W, Y (MenACWY or MPSV4) is currently recommended for HIV-infected MSM (Table 11.1) [60].

Genital ulcer disease is most commonly associated with *T. pallidum* and HSV-2. HSV-1 is also a frequent cause of genital ulcers in MSM [61]. Papular disease is most often caused by human papilloma virus (HPV) but can also be seen with Molluscum contagiosum, a pox virus [62, 63].

Gastrointestinal

Sexually transmitted pathogens can cause disease of both the upper and lower GI tract in MSM. In upper GI tract disease, oropharyngeal manifestations can be broadly categorized as pharyngitis, oropharyngeal ulcers, and oropharyngeal papules/patches. *N. gonorrhoeae* can cause pharyngitis, although typically infection is asymptomatic [64, 65]. *C. trachomatis* can be detected in the oropharynx and transmitted from the oropharynx, but its role in pharyngitis is unclear [66]. Whether transmitted sexually or nonsexually, HSV-1 is also a well-characterized cause of pharyngitis in adolescents and young adults and often occurs concurrently with gingivostomatitis or labial ulcers [64]. Much less commonly, HSV-2 causes an ulcerative pharyngitis [67, 68].

The most common causes of intra-oral sexually transmitted ulcers are HSV-1 and *T. pallidum*. HSV-2 is a rare cause of intra-oral ulcers. The oropharyngeal herpetic lesions of HSV-1 and HSV-2 are indistinguishable on physical examination. They are typically small but may coalesce into larger ulcers or erosions.

Table 11.1 STI vaccination recommendations for HIV-MSM[a]

Organism	Recommendation
Human papilloma virus	• Three dose series through age 26
Hepatitis A	• 2–3 dose series depending upon vaccine if not immune • Some experts recommend waiting until the CD4+ Count $\geq$ 200 cells/μl to vaccinate
Hepatitis B	• Three dose series depending upon vaccine if not immune • Some experts recommend waiting until the CD4+ Count $\geq$ 200 cells/μl to vaccinate
N. meningitidis	• If not previously vaccinated, should receive two-dose primary series of serogroups A, C, W, and Y meningococcal conjugate vaccine at least 2 months apart • Revaccinate every 5 years • Vaccination against serogroup B is not routinely recommended • Some experts recommend waiting until the CD4+ Count $\geq$ 200 cells/μl to vaccinate

[a]Created based on data from [60]

They typically have erythematous borders with a white base and are associated with mild discomfort to frank pain. In contrast, the intra-oral ulcer (chancre) of primary syphilis is typically solitary and painless (see Fig. 11.2). Secondary syphilis may also affect the oropharynx and should be considered in persons presenting with oral lesions including ulcers [69]. Sexually transmitted intra-oral papules are caused by some types of human papillomavirus [70]. Oral HPV-lesions are classically soft, pink-to-white growths most commonly observed on the buccal mucosa and soft palate but can also occur on the tongue and lips (Fig. 11.3) [70].

In STI-related lower GI tract disease, the anus, rectum, and/or colon may be involved. Clinical STI manifestations of the anus occur as ulcer disease and papules. Perianal ulcers are typically caused by HSV-2, *T. pallidum* and with increasing frequency HSV-1 in MSM. The perianal ulcers of HSV-1 and HSV-2 are indistinguishable. Perianal and anal papules are most often caused by HPV. They are typically described as pink or gray fleshy cauliflower like growths. They may extend into the anal canal and be palpated on digital rectal examination or observed by anoscopy [71]. Condyloma lata of secondary syphilis can involve the anus and perianal skin and can be confused with condyloma accuminatum. Condyloma lata typically presents with multiple moist, flat lesions whereas condyloma accuminatum are typically raised. Further, the natural history of each is different with condyloma accuminatum presenting subacutely and condyloma lata presenting more acutely. Other anal findings that may raise concern for the patient or the provider include skin tags, hemorrhoids, abrasions, and plaques associated with local trauma (including overwiping) or systemic disease. When the etiology of anal lesions is unclear, the provider should refer the patient to either a dermatologist or gastrointestinal specialist.

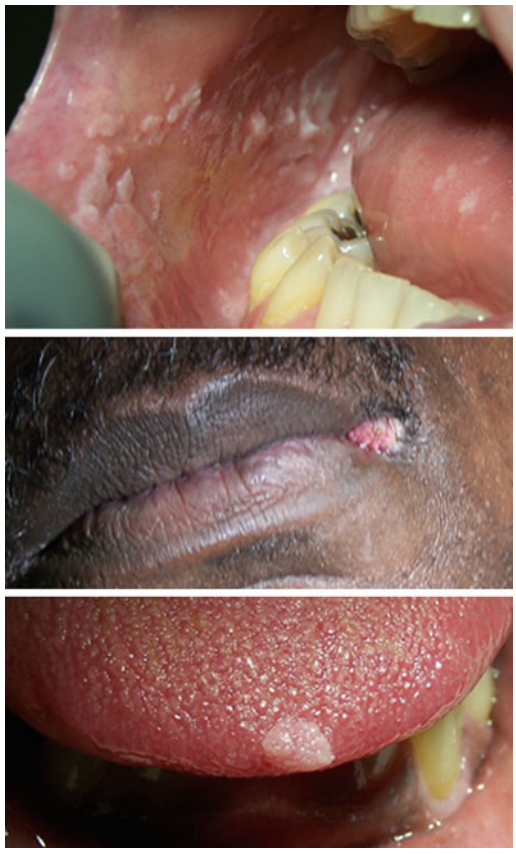

Fig. 11.3 Examples of HVP-oral lesions. Courtesy of Jeffery D. Hill, DMD

STI involving the rectum, rectum and colon, and small intestine can manifest as proctitis, proctocolitis, and enteritis, respectively. Proctitis refers to inflammation of the rectum. Symptoms and signs associated with acute proctitis include mucopurulent anal discharge, anorectal bleeding, constipation, tenesmus, and a sensation of rectal fullness or of incomplete defecation. Mucous streaking of the stool, constipation, or the sensation of incomplete defecation may indicate mild acute or chronic proctitis while anal discharge, anorectal bleeding and tenesmus indicate more severe proctitis [72, 73]. *C. trachomatis* (including LGV serovars, see below), *N. gonorrhoeae*, HSV-2, HSV-1 and *T. pallidum* are common causes of proctitis typically acquired through receptive anal sex [65, 74]. Emerging evidence suggests that *M. genitalium* may also cause proctitis [75, 76].

Proctocolitis refers to inflammation of rectum and colon. In addition to the signs and symptoms associated with proctitis, patients with proctocolitis may describe small volume diarrhea,

bloody stool, abdominal tenderness/pain and abdominal cramping [72]. Typical pathogens are acquired through receptive anal sex or through oral-anal contact. *Campylobacter* sp, *Shigella* sp, *Entamoeba histolytica*, and LGV serovars of *C. trachomatis* are causes in MSM [77–83]. Cytomegalovirus and other opportunistic pathogens (regardless of route of infection) should also be considered in persons with advanced HIV [65].

For MSM presenting with symptoms of proctitis or proctocolitis, anoscopy allows for direct visualization of the rectal mucosa. Mucous in the rectal lumen, mucosal edema, friability, easy bleeding, or ulceration may be present. Anoscopic specimen collection should include Gram stain to evaluate for Polymorphonuclear (PMN) cells and the intracellular diplococci of *N. gonorrhoeae*, a swab specimen for nucleic acid amplification tests (NAAT) for *C. trachomatis* and *N. gonorrhoeae*, and a swab specimen for HSV culture or PCR (both HSV-1 and HSV-2). Blood for syphilis serologies should also be obtained. Since diagnostic tests typically require more than 24 h to complete, empiric therapy should be given to cover the most likely pathogens [72].

Enteritis refers to inflammation of the small intestine and is characterized by symptoms that include large volume, watery diarrhea, bloody stool, abdominal cramping, and nausea with or without vomiting. STI pathogens commonly associated with enteritis in MSM include: giardia, campylobacter, and salmonella, but may include other organisms that are transmitted through oral-anal exposure. Systemic symptoms may include malaise, fever, and weight loss. With enteritis, there is typically a marked absence of proctitis or proctocolitis (unless concurrent infection with a second pathogen). Sexual history should be explored in MSM presenting with symptoms of enteritis.

In most cases, the clinical manifestations of STI in HIV-infected and HIV-uninfected MSM are similar. This is particularly true for HIV-infected MSM who are virologically suppressed on ART. However, a subset of MSM with HIV and low CD4+ T cell counts may present with more severe and/or atypical clinical manifestations of STI. As examples, HSV-2 in persons with advanced HIV may present as chronic mucocutaneous ulcers that last weeks to months. These ulcers may be extensive and difficult to treat [84, 85]. Other rare atypical manifestations of HSV-2 reported in persons with advanced HIV include slow growing nodular, tumoral or verrucoid masses that mimic penile or anal neoplasms [86]. Primary syphilis more frequently presents with multiple ulcers in patients coinfected with HIV than those with primary syphilis alone [87]. Immunosuppressed HIV-infected MSM may also be at increased risk for neurosyphilis. Genital ulcers are also more likely to be present during secondary syphilis in HIV-coinfected patients [88]. The influence of HIV on clinical manifestations is discussed in the context of the specific pathogen in the following sections.

Epidemiology, Diagnostics, and Treatment of STI in Msm

STI are common and on the rise in some subpopulations of MSM [89, 90]. In the following sections, the prevalence of specific pathogens including genital and extragenital infections is presented. This is followed by a discussion of clinical manifestations, diagnosis, and treatment of each STI. Special considerations related to the pathogen, its diagnosis, and/or treatment in MSM are presented.

Bacterial Pathogens Causing Oropharyngeal, Urethral, and Rectal Infection

Neisseria Gonorrhoeae

N. gonorrhoeae is common and increasing in MSM [6, 91–96]. Although the absolute number of infections is higher among MSW and women who have sex with men, the proportion *of N. gonorrhoeae* cases in MSM compared to these other groups is higher and demonstrates a substantial and growing inequality in the burden of STI in MSM [97]. A recent surveillance study of

MSM presenting to STI clinics in the U.S. reported a median site-specific *N. gonorrhoeae* prevalence of 19.0% and the burden of *N. gonorrhoeae* was greater among HIV-infected than HIV-uninfected MSM (Urethral gonorrhea: HIV-infected = 11.3%, HIV-uninfected = 6.8%; pharyngeal gonorrhea: HIV-infected = 9.2%, HIV-uninfected = 7.7%; rectal gonorrhea: HIV-infected = 17.1%, HIV-infected = 7.3%) [98]. The majority of MSM with oropharyngeal or rectal *N. gonorrhoeae* do not have concurrent urethral *N. gonorrhoeae* infection. Thus most cases of *N. gonorrhoeae* in MSM will be missed with urethral screening alone [6]. This highlights the importance of routine extragenital screening in MSM.

When symptomatic, symptoms caused by *N. gonorrhoeae* typically appear 72 h to 2 weeks after exposure [99]. The presentation of gonococcal urethritis in MSM is similar to that occurring in MSW and is described elsewhere in this book. Pharyngitis caused by *N. gonorrhoeae* is characterized by sore throat and in some cases with tonsillar involvement [64, 65]. A whitish-yellow exudate has been reported in a minority of patients with tonsillar involvement [100]. Fever and cervical lymphadenopathy are uncommon [64]. The typical mode of acquisition is receptive oral sex. Because the symptoms of gonococcal pharyngitis are nondescript and difficult to distinguish from other causes of pharyngitis, a thorough history that includes sexual exposures should be obtained from MSM presenting with symptoms of pharyngitis. Pharyngitis caused by *N. gonorrhoeae* is the exception with most infections of the pharynx being asymptomatic [6, 94, 101]. NAAT are the preferred diagnostic assays [65].

Proctitis and proctocolitis caused by *N. gonorrhoeae* are difficult to distinguish from other causes based upon symptoms and direct visualization of the rectal mucosa by anoscopy. However, a clue for proctitis caused by *N. gonorrhoeae* is the presence of a thick purulent discharge expressed from the anal crypts [99]. Gram stain may reveal intracellular diplococci but their absence does not exclude *N. gonorrhoeae* as the cause. Like pharyngeal infections, rectal infections with *N. gonorrhoeae* are often asymptomatic and screening in asymptomatic men is required to find infection [94, 102, 103].

Because of their high sensitivity and specificity, NAAT are the preferred diagnostics for *N. gonorrhoeae* [104]. NAAT for *N. gonnorrhoeae* is often performed concurrently with NAAT for *C. trachomatis* [65]. Urethral infection can be diagnosed from a provider-collected urethral specimens or from first void urine. Although not FDA approved for rectal or oropharyngeal specimens, NAAT is highly effective and can be used for diagnosis of extragenital *N. gonorrhoeae* infection in laboratories with Clinical Laboratory Improvement Amendment (CLIA)-defined performance specifications [104–106]. Self-collected rectal specimens are comparable to provider-collected specimens and may be more acceptable to patients [107, 108]. Extragenital screening is critical to finding the majority of infections in MSM.

N. gonorrhoeae has developed resistance over time to all antimicrobial regimens recommended for its treatment, though multidrug resistant gonorrheae is uncommon at present [109–120]. MSM are particularly vulnerable to infection with resistant gonorrhoeae [114, 121–125]. Several factors may contribute to the higher rates of infection with resistant strains among MSM. The oropharynx, a common site of infection in MSM, is potentially an important site for the development of resistance, sometimes through plasmid exchange with commensal *neisseriae* [126]. Studies also suggest that mechanisms that provide antimicrobial resistance may also allow for improved survival of *N. gonorrhoeae* in the rectum [127–129]. Higher rates of antimicrobial use among MSM when compared to MSW may also contribute to the selection and persistence of resistant *N. gonorrhoeae* [124]. New patterns of *N. gonorrhoeae* antimicrobial resistance have often been reported internationally prior to their presentation in the U.S [130, 131]. Some MSM may be more likely to travel internationally and report foreign-borne sex partners which may facilitate entry of resistant *N. gonorrhoeae* into the U.S. [132]. Sexual behaviors of some MSM include group sex and circuit parties that may

allow for contact between MSM from various geographic regions and facilitate spread of resistant *N. gonorrhoeae* [133–135].

Due to *N. gonorrhoeae's* propensity for rapid development of antimicrobial resistance local resistance patterns in MSM (when available) should be considered when selecting therapy [136]. Most guidelines recommend dual therapy with ceftriaxone 250 mg IM as a single dose plus azithromycin 1 g orally for uncomplicated infections of the urethra and rectum [65, 137]. The recommended alternative regimen is cefixime 400 mg orally as a single dose plus azithromycin 1 g as a single dose and should only be used if ceftriaxone is unavailable, because of emerging resistance to cefixime and its proven lower efficacy [65, 138]. The underlying philosophy for dual therapy is that use of two antibiotics with different mechanisms of action may improve treatment efficacy and slow development of further resistance [65]. Azithromycin is preferred over doxycycline because of *N. gonorrhoeae's* higher resistance to doxycycline and because of the ease of dosing of azithromycin [65, 114]. Alternative regimens are available and may be used for rectal infections in MSM who cannot tolerate first line agents. Recommended treatment regimens are the same regardless of HIV status. Test of cure for urethral or rectal *N. gonorrhoeae* infection in MSM is not currently recommended [65]. However, surveillance for *N. gonorrhoeae* antimicrobial resistance is ongoing and recommendations are updated according to new trends in its resistance [139]. Retesting of persons with uncomplicated urethral or rectal gonorrheae, is recommended 3 months after treatment whenever possible in sexually active MSM [65].

Gonococcal infections of the pharynx are more difficult to eradicate than urethral or rectal infections [140]. When treated with the preferred regimen of Ceftiaxone plus azithromcyin, no test of cure is required. However, if treated with an alternative regimen, test of cure for pharyngeal infection by NAAT or culture is recommended 14 days after treatment to ensure eradication of infection [141]. If a NAAT alone is used for test of cure and is positive, confirmatory culture should be performed prior to retreatment. Positive cultures should undergo antimicrobial susceptibility testing [65]. Gonococcal culture and susceptibility testing should be performed on any patient with persistent symptoms after treatment. Further treatment decisions should be made by an infectious diseases expert and the public health system notified. Recommended treatment regimens and follow up are the same regardless of HIV status. Because *N. gonorrhoeae* infection is often asymptomatic at both genital and extragenital sites, routine screening is recommended in MSM (Table 11.2).

Chlamydia Trachomatis

Like *N. gonorrhoeae*, *C. trachomatis* is highly transmissible and common in MSM [6, 102, 142]. The U.S. STD Surveillance for 2015 showed similar rates of urethral chlamydia in MSM regardless of HIV status but much higher rates of rectal chlamydia among HIV-infected MSM presenting to STD clinics for care (urethral chlamydia: HIV-infected: 5.6%, HIV-uninfected: 6.4%; rectal chlamydia: HIV-infected: 18.6%, HIV: uninfected 8.1%) [98]. Although pharyngeal infection does occur, its clinical significance is not known and routine screening is not recommended [65]. In prevalence studies of MSM, anorectal chlamydia is more commonly observed than urethral or pharyngeal chlamydia [6, 93, 143, 144]. However, evidence suggests that *C. trachomatis* is transmissible from the oropharynx and may serve as reservoir for the organism; and some experts support pharyngeal screening in MSM [145, 146].

Genital and extragenital *C. trachomatis* infection is most often asymptomatic and may be present for extended periods of time [91, 94, 145, 147, 148]. Only about 10% of infected men are thought to develop symptoms and routine screening is recommended in MSM (see Table 11.2) [149]. When symptoms occur, their timing is not well defined but may be delayed until weeks after infection given the slow replication cycle of *C. trachomatis*. Symptomatic urethritis caused by *C. trachomatis* typically presents with a mucoid or watery urethral discharge and dysuria. Symptomatic rectal infection

Table 11.2 STI screening recommendations for HIV-Infected MSM[a]

Organism	Screening recommendation
C. trachomatis	• For sexually active MSM, screen at the first HIV evaluation at sites of exposure (urethra and/or rectum) regardless of condom use • Screen at least annually at sites of contact regardless of condom use • Screen more frequently (every 3–6 months) at sites of contact if at increased risk
N. gonorrhoeae	• For sexually active MSM, screen at the first HIV evaluation at sites of exposure (pharynx, urethra, and/or rectum) regardless of condom use • Screen at least annually at sites of contact regardless of condom use • Screen more frequently (every 3–6 months) at sites of contact if at increased risk
T. pallidum	• For sexually active MSM, screen at first HIV evaluation • Screen at least annually • Every 3–6 months if at increased risk
Herpes simplex viruses	• HSV-1 and HSV-2 type-specific testing should be considered for persons presenting for STI evaluation
Hepatitis B virus	• Screen for HBsAg and anti-HBc and/or anti-HBs
Hepatitis C virus	• Screen at the initial HIV evaluation • Screen annually

[a]https://www.cdc.gov/std/tg2015/screening-recommendations.htm 2015 STD treatment guidelines

with non-Lymphogranuloma Venereum strains of *C. trachomatis* typically presents as a mild proctitis [150].

As for *N. gonorrhoeae*, NAAT are the preferred diagnostics for chlamydia and are often combined with NAAT for other STI [65, 104]. Specimen collection is similar for *C. trachomatis* as described for *N. gonorrhoeae* including rectal specimens.

Azithromycin 1 g orally as a single dose and doxycycline 100 mg orally twice a day for 7 days are highly effective for the treatment of urogenital *C. trachomatis* infection [151]. Head-to-head comparisons of azithromycin and doxycycline in the treatment of rectal chlamydia are lacking. However, retrospective studies suggest high rates of treatment failure with azithromycin when compared to doxycycline [152, 153]. For MSM presenting with acute proctitis (and without concern for LGV, see below), doxycycline 100 mg twice daily for 7 days is preferred over azithromcyin for empiric treatment of *C. trachomatis*. As stated previously, the clinical relevance of oropharyngeal chlamydia is poorly understood and routine screening for oropharyngeal chlamydia is not recommended. However, because *N. gonorrhoeae* and *C. trachomatis* assays are often linked, asymptomatic oropharyngeal *C. trachomatis* infection is not infrequently identified in MSM. When identified, it should be treated with either azithromycin or doxycycline as outlined for urogenital infection [65]. Treatment of *C. trachomatis* infection in MSM is the same regardless of HIV status [151].

Lymphgranuloma Venereum

LGV has increased at a concerning rate among MSM and in particular among HIV-infected MSM [154, 155]. LGV is caused by *C. trachomatis* invasive serovars L1, L2, and L3 [83]. In male genital infection, LGV presents as a transient genital ulcer disease associated with inguinal/femoral lymphadenopathy [156]. Underscoring its invasive nature, if left untreated, LGV may lead to chronic complications including deep tissue abscess, strictures, fissures, and chronic pain [83]. More recently, LGV has become a leading cause of proctitis and proctocolitis in MSM in developed countries [83]. The range of prevalence of LGV in persons with proctitis and proven rectal chlamydia is 7–23% [83, 157]. Proctitis and proctocolitis caused by LGV associated serovars can be severe, mimicking inflammatory bowel disease, with symptoms that include mucoid and/or hemorrhagic rectal discharge, anal pain, constipation,

and tenesmus, or hematochezia [158–160]. Prolonged infection can result in systemic symptoms including fever, malaise, and weight loss as well as serious complications including perirectal abscesses, fissures, and fistula formation [83]. When gram-stained, anal discharge in persons with LGV proctitis is likely to show white blood cells but no organisms [157]. Erythematous, friable ulcers are frequently observed on colonoscopy [83]. Although LGV rectal infection causes a more severe proctitis and proctocolitis than other *C. trachomatis* serovars, LGV can be asymptomatic [161].

Definitive laboratory diagnosis depends on detecting *C. trachomatis* DNA followed by genotyping to specifically detect LGV-specific serovars. However, assays to detect LGV-specific serovars are currently only found in research labs and are not commercially available. In the clinical setting, the diagnosis is typically based on the epidemiological and clinical findings consistent with LGV, confirmation of *C. trachomatis* by NAAT, and exclusion of other causes of symptoms [83].

Doxycycline 100 mg twice daily for 21 days is the treatment of choice for LGV proctitis [65, 83]. The prolonged length of therapy is required because of the invasiveness of LGV and the difficulty with its eradication. HIV-infected persons with LGV proctitis or proctocolitis respond well to doxycycline. However, some may have delayed resolution of symptoms. In these cases, patients may benefit from an extended course of doxycline [83]. Erythromycin, azithromycin, and moxifloxacin have activity against LGV but efficacy data are limited and side effect profiles may compromise their use [162–164].

Syphilis

Rates of syphilis are high and have been consistently increasing in MSM [98]. Of all cases of Primary and Secondary Syphilis reported in men in the U.S. in 2015, MSM accounted for 82% [98]. Similarly, high trends of Primary and Secondary Syphilis in MSM are reported in both developed and developing countries with HIV-infected MSM more often affected [165–167]. Reinfection is common in HIV-infected MSM [168, 169]. Not only is syphilis common in HIV-infected men, it is also an important predictor for new acquisition of HIV [170, 171].

The broad range of clinical manifestations associated with primary, secondary, and tertiary syphilis are covered in detail elsewhere in this book. Most HIV-infected patients with *T. pallidum* present with the typical dermatologic manifestations of primary and secondary syphilis. However, notable differences have been observed. As mentioned, in HIV-infected individuals, primary syphilis more frequently presents with multiple ulcers and genital ulcers are more likely to be present during secondary syphilis [87, 88]. Atypical chancres have been reported but are uncommon [172–174]. Unusual rashes in secondary syphilis have also been reported in patients with HIV but also in patients who are HIV-negative [175–179]. It remains unclear whether the presence of HIV influences the rash of secondary syphilis. Neurosyphilis can occur at any stage of infection. HIV-infected persons with early syphilis appear to possibly have an increased risk for developing neurological involvement [180]. Ocular syphilis, a type of neurosyphilis, may also occur with greater frequency in HIV-infected patients. Ocular syphilis can involve any part of the eye but panuveitis and posterior uveitis are the most common types of ocular inflammation documented [181]. Common signs and symptoms include eye redness, blurred vision, and vision loss. Other possible symptoms include eye pain, floaters, flashing lights, eye pressure, and photophobia [182]. Ocular syphilis may not be accompanied by manifestations of neurosyphilis or positive cerebrospinal fluid findings [183, 184]. Thus, ocular syphilis should be considered in MSM at risk for syphilis and presenting with eye complaints with or without other findings consistent with neurosyphilis. Although the skin, mucous membranes, and CNS are most frequently involved, syphilis is a systemic disease and can affect any organ system. A high index of suspicion should be maintained when assessing MSM at risk for syphilis who present with symptoms involving other organs systems.

As with all STI, a careful history and physical examination are central to interpreting risk and identifying clinical manifestations of syphilis. In MSM, the painless primary lesion may involve the mouth or rectum and go unnoticed by the patient and the provider. The cutaneous rash and mucous patches may be subtle and resolve without treatment. Because syphilis is characterized by periods of latency, many infected persons will have no evidence of infection at the time of their healthcare visits supporting the need for routine screening (see Table 11.2).

Laboratory diagnosis of syphilis requires two steps, a nontreponemal and a treponemal test. Nontreponemal tests include the Venereal Disease Research Laboratory (VDRL) and the RPR assays. Both are equally valid but not directly comparable because RPR titers are often slightly higher than VDRL titers. Nontreponemal antibody titers correlate with disease activity in most cases and are used to both diagnose and follow treatment response. A fourfold change in titer in the 6 months posttreatment is considered initial evidence of a successful response to therapy. However, lack of a fourfold change does not necessarily indicate treatment failure. With treatment, nontreponemal tests usually decline and may become nonreactive. False positives are possible with nontreponemal tests and thus require confirmation with Treponemal tests. False positive nontreponemal tests may be more common in people with autoimmune diseases, and multiparous women. In some parts of the world, infection with non-syphilitic treponemes (e.g., Pinta, Bejel) may result in biological false positive tests. The treponemal tests most often used are the fluorescent treponemal antibody absorbed (FTA-ABS) and the *T. pallidum* passive particle agglutination (TP-PA) assays. These tests are qualitative and typically remain positive throughout life. The sensitivity of treponemal and nontreponemal tests increases with duration of infection ranging from 75% in primary syphilis to virtually 100% in secondary syphilis. The clinician should take this into account when evaluating patients with findings concerning for syphilis. In late syphilis the treponemal test almost always remains positive while nontreponemal tests may decline with time. With the development of automation, some laboratories invert the classic algorithm and first test with a treponeme-specific test and confirm with a non-treponemal test.

The diagnostics used for syphilis are the same regardless of sex, sexual behavior, or HIV status. For most patients with HIV, these assays are accurate for diagnosing and monitoring treatment of syphilis. However, interpretation of these tests in the diagnosis and when following treatment can be more complicated in HIV-infected persons.

Genital Herpes

Genital herpes is the major cause of genital ulcer disease world worldwide [185]. It's primary cause is HSV-2 and is most often transmitted through anogenital-anogenital contact. HSV-2 is common in several studies of MSM and observed with high frequency among HIV-infected MSM [186–188]. In addition, HSV-1 is increasingly observed among young MSM as the cause of genital herpes, often reflecting oral-genital contact [189]. Genital HSV-1 infection is believed to recur at lower frequency than HSV-2 [190, 191]. However, the anogenital clinical manifestations of HSV-1 and HSV-2 are indistinguishable and require laboratory tests to identify the responsible virus. The major mode of transmission of HSV-1 is thought to be oral-anogenital contact but penile-anogenital transmission is also thought to be possible. Active genital herpes is an important risk factor for acquisition of HIV [192, 193]. Furthermore, HIV transmission to others is believed to be increased by HSV-2 coinfection [185].

Genital herpes is characterized by life-long infection and recurrent episodes. Classic and atypical manifestations of first-episode and recurrent genital herpes are covered elsewhere in detail and do not differ between MSM and MSW. However, MSM are more likely to have anorectal exposure and herpes simplex infection should be considered in MSM presenting with anal pain, perianal lesions, and proctitis [72, 74]. Reactivation of genital herpes in persons with HIV and who are immunosuppressed can be more severe,

of longer duration and occur more frequently than in the immunocompetent host [185]. Persons with HIV–HSV-2 coinfection not receiving ART also have higher rates of subclinical reactivation and asymptomatic viral shedding. CD4+ T cell count inversely correlates with rates of shedding [194]. High rates of HSV-2 shedding and clinical disease are seen in coinfected persons during the first 3–6 months after initiating ART and may represent an immune reconstitution syndrome [195]. Limited studies suggest that ART, in persons with well-controlled HIV, reduces the frequency of genital herpes recurrence. However, ART appears to have less effect on asymptomatic shedding of HSV-2 [196].

The diagnostic approach to genital herpes depends on the presence and stage of clinical manifestations at the time of presentation for care. Cell culture and NAAT are preferred when genital ulcers or other mucocutaneous lesions are present [65]. NAAT are more sensitive than culture. However, the use of cell culture or nucleic acid amplification is often determined by availability within the healthcare system. When cell culture is used, the practitioner should maintain a high level of suspicion even when cultures are negative especially when assays for other causes of genital ulcers are nonrevealing [197]. Type-specific serologic tests can be used alone or in combination with viral tests (when lesions are present) to interpret cause and proximity of infection. Because several weeks is required for antibodies to develop, persons presenting with genital lesions and a positive cell culture or nucleic acid amplification test but negative type-specific serologic tests have early infection. The presence of type-specific positive cell culture or nucleic acid amplification plus a positive serologic test suggest long standing infection with recurrence [197]. Serologic tests alone may be useful in persons with recurrent anogenital symptoms in whom HSV PCR or culture are negative, in persons who carry a clinical but unconfirmed diagnosis of genital herpes, or in persons who have a partner with genital herpes. In these cases, if serologic tests are positive for HSV-2, the provider can be relatively assured that the patient has genital infection. For HSV-1, seropositivity alone does not distinguish orolabial from anogenital infection [65].

Serologic test performance overall is good but reduced sensitivity and/or specificity is reported in some populations including persons with HIV [198, 199]. To optimize sensitivity and specificity of HSV-2 serologic assays, experts recommend using a higher than-standard-index cutoff [200].

Screening for HSV-1 and HSV-2 is not recommended in asymptomatic adolescents and adults [201]. However, some experts suggest a benefit to screening persons with HIV and MSM at increased risk for acquiring HIV (see Table 11.2). Since genital herpes is a well-characterized risk factor for HIV acquisition, knowledge of genital herpes may lead to behavioral modifications that reduce the risk of acquiring HIV and also of transmitting HSV-2 [202]. Of note, daily suppressive therapy with a thymidine kinase inhibitor (TKI) (acyclovir) in HIV–HSV-2 coinfected persons did not reduce transmission of HSV-2 to susceptible partners [203]. This is in contrast to observations in HIV-uninfected persons in which daily suppressive therapy with a TKI (valacyclovir) reduced HSV-2 transmission to sexual partners by almost 50% [204]. Studies also suggest that HSV-2 may increase infectiousness of HIV while daily suppressive TKI reduces HIV viral load and HIV infectiousness [205–207]. Despite these findings, daily suppressive therapy with TKIs does not reduce HIV transmission [208]. These studies were performed in heterosexuals but suggest that TKI would also have limited benefit in reducing transmission of either HIV or HSV-2 from coinfected MSM to their sexual partners.

Antiviral therapy is available for the treatment of clinical episodes and for suppression of recurrences in persons with frequent outbreaks. Recommended agents include the TKIs acyclovir, valacyclovir, and famciclovir. Dosing varies by indication (i.e., first clinical episode, recurrence, or suppression) and is covered elsewhere. For persons with HIV, recommended regimens for recurrent infection and suppression differ in dosage and length of therapy [65].

Thymidine kinase resistance is more commonly observed in immunocompromised persons, including those with HIV and should be considered in immune-compromised persons who do not respond to treatment [209]. When concern for resistance arises, a viral isolate should be obtained for culture and resistance testing [85]. Foscarnet is often an effective treatment in thymidine kinase resistant HSV-2 [210]. Cidofovir and imiquimod are alternative options [211].

Human Papillomavirus

Sexual transmission of human papillomaviruses is very common with approximately 40 different types of HPV that infect the anogenital and upper digestive tract [212, 213]. Low risk HPV types cause anogenital and upper digestive tract warts and mild dysplasia whereas high-risk HPV types can cause high grade dysplasia with progression to anogenital, penile, and oropharyngeal cancers [214]. Incidence of genital HPV infection is similar between MSM and MSW [215]. Genital warts also occur at similar rates in MSM and MSW [63]. In contrast, detection of anal infection is more common in MSM and reported prevalence is between 42 and 72% while oropharyngeal infection is between 3 and 11% and penile infection is between 15 and 18% [216–219]. The burden of HPV-associated manifestations at the anus, including cancer, is higher in MSM. HIV-positive MSM carry the highest burden of HPV including high-risk HPV types and suffer a higher prevalence of HPV-associated malignancies [186, 216, 220].

Many HPV infections are subclinical, and self-limited [221]. Routine screening for HPV in asymptomatic patients, including MSM, using molecular methods is not recommended. Clinical manifestations of HPV include oral and anogenital warts the majority of which are caused by the non-oncogenic HPV types 6 and 11. Oral and anogenital warts are usually asymptomatic but may cause pain and itching depending upon size and location. Intra-anal warts are seen most often in persons who have receptive anal sex and may not be visible on external inspection but palpated on digital rectal examination [65]. Anogenital warts are typically diagnosed based upon clinical appearance [221]. Molecular testing for HPV in persons with anogenital warts is not required. In support, among MSM requiring surgical removal of anogenital warts, intraepithelial neoplasia or squamous cell carcinomas were identified in the excised tissue in 26% of HIV-negative MSM and 47% of HIV-positive MSM [222]. With these high rates of intraepithelial neoplasia and squamous cell carcinomas, providers should maintain a low threshold for biopsy of anogenital warts, especially in immune-compromised persons. Any atypical lesion, characterized by pigmentation, induration, fixation to underlying tissue, bleeding or ulceration, should undergo biopsy [221]. Digital rectal examination may reveal palpable lesions. When lesions are palpated but not visualized, further evaluation is warranted, especially among HIV-infected MSM. Referral for anoscopy, with direct visualization and excision is recommended.

Several treatment options are available for treatment of anogenital warts. Choice of treatment is determined by wart characteristics (size, number, location) and patient/provider preference (cost, convenience, adverse effects) [65]. Efficacy is similar between treatments.

Despite higher prevalence of squamous cell carcinoma of the anus in MSM particularly those who are HIV-infected, data are currently insufficient to recommend routine screening. Large prospective studies are underway to better define when and how often to test for anal cytology in MSM. Although abnormal anal cytology is easily identified, its significance is not well-understood. One recent study reported abnormal anal cytology in 25% of HIV-uninfected MSM and higher prevalence among HIV-infected MSM that inversely correlated with CD4+ T cell count (47% among HIV-positive MSM with CD4 count <350 cell/mm). However, repeat screening in MSM with abnormal anal cytology, including high grade squamous intraepithelial lesions, showed regression of the abnormal anal cytology in the majority of cases [223]. Further confounding, anal intraepithelial neoplasia may occur in the absence of abnormal cytology [224].

Further studies are needed to establish if there is a benefit to anal cancer screening in MSM and which screening modality(ies) is best.

HPV vaccination is highly effective and widely available. Quadrivalent and nine-valent forms are licensed and available for use in males. These vaccines target the HPV types commonly associated with genital warts and with cancer. HPV vaccination is recommended through age 26 year for MSM (regardless of HIV status) who have not been previously vaccinated (see Table 11.1) [225]. Although the epidemiology suggests that many older MSM may be susceptible to one or more of vaccine-targeted HPV types, vaccination of MSM over the age of 26 years is not recommended at this time, but studies are underway to determine if there may be some benefit.

Hepatitis A

The Hepatitis A Virus (HAV) is a single-stranded RNA virus that is most commonly transmitted by the fecal-oral route. It infects the oral mucosa, survives in the intestine, and then infects the liver. Replication occurs in the liver and is transported by the biliary system to the intestinal tract where it is shed in the feces [226]. In most cases, HAV causes a self-limited illness most commonly characterized by fevers, malaise and jaundice [227]. Rarely, HAV causes fulminant liver failure and death. In high-income countries MSM are more likely to test positive for Hepatitis A antibodies than the general population and the likelihood of having antibodies to HAV correlates with the number of same-sex sex partners and time since same-sex sexual debut [228]. Numerous outbreaks of HAV have been reported in MSM [229–231]. In MSM with HIV, peak HAV viral loads and duration of viremia are longer [232].

The diagnosis of acute Hepatitis A requires serologic confirmation through detection of serum immunoglobulin (Ig) M anti-HAV antibodies. Anti-HAV IgM antibodies are present at the time of symptom onset and can persist for 3–6 months. Anti-HAV IgG antibodies appear in the convalescent phase, persist for decades, and are associated with life-long protective immunity. There is no treatment for hepatitis A and care is supportive [233]. Effective prophylactic vaccines are available for Hepatitis A and vaccination is recommended for MSM (see Table 11.1) [234]. Durability of the serological response to Hepatitis A vaccination is impaired in HIV-infected persons, especially persons with low CD4+ T cell counts [235]. Although not currently recommended, long-term durability of response in HIV-infected persons is better with 3 rather than 2 doses of HAV vaccine [236].

Hepatitis B

The Hepatitis B Virus (HBV) is a partially double-stranded DNA virus that is found in blood and other body fluids including semen [237]. In MSM, the rates of infection far exceed those in the general population and are mediated by unprotected anal sex [228]. The incubation period from exposure to symptoms varies from 6 weeks to 6 months [65]. HBV infection can be self-limited or chronic. The clinical presentation of HBV varies from asymptomatic to fulminant hepatitis and liver failure. About half of newly acquired HBV infections are believed to produce symptoms and in rare cases leads to acute liver failure [238]. The likelihood of developing chronic hepatitis B inversely correlates with age of infection. Chronic hepatitis B is more common in MSM, particularly HIV-infected MSM [239]. In MSM, 6–10% of HBV-infected men are coinfected with HIV [240]. In the HIV–HBV coinfected and untreated individual, HBV is more rapidly progressive. The HbsAg carrier rates and HBV viral loads are higher and episodes of HBV activation are more frequent in HIV-infected individuals than those who are HIV-uninfected. End-stage consequences of HBV infection including cirrhosis and hepatocellular carcinoma are also more frequent in HIV-infected MSM [240].

The diagnosis of both acute Hepatitis B, chronic Hepatitis B, and immunity to Hepatitis B (either through resolved infection or through

vaccination) is based on interpreting serologic markers for HBV. The presence of Hepatitis B surface antigen (HBsAg) indicates active infection. The presence of anti-Hepatitis B core IgM helps distinguish acute from chronic infection. The presence of anti-Hepatitis B surface antibodies (Anti-HBs) indicates immunity to Hepatitis B. In combination with total anti-Hepatitis B core antibody (Total anti-HBc), the presence of anti-HBs Ab mean recovery from past infection and immunity. The presence of anti-HBs Ab alone is consistent with immunity after immunization [239]. No treatment is available for acute hepatitis B. However, treatment is available for chronic hepatitis B. As a priority, adults, adolescents and children with chronic hepatitis B and clinical evidence of compensated or decompensated cirrhosis should be treated. Treatment is also recommended for adults over 30 years of age with chronic Hepatitis B without clinical evidence of cirrhosis, who have elevated alanine transferase and high level of HBV replication. For HBV monoinfected person, nucleos(t)ide analogs with a high barrier to drug resistance including tenofovir or entecavir are recommended. All HBV and HIV-coinfected individuals should be treated for both HIV and HBV [241]. Tenofovir plus emtricitabine or lamivudine as a part of the antiretroviral regimen will concurrently treat HIV and HBV, and need to be used for life to avoid HIV rebound and hepatic inflammation from HBV [241].

Universal vaccination of children and adolescents against HBV has helped reduce the burden of HBV infection. However, some groups including MSM remain at risk and, if unvaccinated, they should receive the HBV vaccine series [65, 234]. The HBV vaccine is also recommended for all persons living with HIV (see Table 11.1) [234]. Lower HBsAb seroconversion rates after vaccination are observed in persons with HIV. Further, in those who do respond to vaccination, rapid declines in antibody titers are observed more often in persons with HIV [242–244]. It is recommended that persons with HIV infection should be tested for anti-HBsAb 4–8 weeks after completing the vaccination series [65]. Although not yet included in guidelines, new studies suggest that immune responses to HBV vaccination are improved by higher concentrations and by increased number of doses in the vaccine series in persons with HIV [245]. Clinicians may want to recheck HBsAb levels periodically in HIV-infected patients who engage in condomless sex.

Hepatitis C

Hepatitis C Virus (HCV) is a single-stranded RNA virus and primarily considered to be a blood–borne pathogen transmitted through exposure to blood through needle-sharing, transfusion of contaminated blood products and unsafe medical practices [246]. Worldwide the most common mode of transmission is intravenous drug use (IDU) [247]. However, among HIV-infected MSM, increasing rates of HCV infection have been observed and are believed to represent sexual transmission [246]. Supporting sexual transmission, IDU is reportedly low in cohorts of HIV–HCV coinfected MSM and high-risk sexual behaviors (i.e., unprotected anal sex and fisting), concurrent diagnosis of chlamydia, and methamphetamine use are linked to HCV infection [248, 249]. Further supporting sexual transmission, HCV is shed in ejaculate and from the rectum (even in the absence of rectal bleeding) at sufficient levels to cause infection, though concentrations in blood are generally higher [250, 251]. Rates of reinfection are also high in HIV-infected MSM successfully treated for HCV who continue to engage in mucosally traumatic sex and methamphetamine use during sex [249]. While sexual transmission of HCV occurs among HIV-infected MSM, sexual transmission in non-IDU, HIV-uninfected MSM remains uncommon [246]. The factors that result in higher rates of HCV transmission in HIV-infected MSM are incompletely understood but thought to be related to both biological and behavioral factors. Biologically, HIV leads to chronic gastrointestinal inflammation weakening the mucosal immune system and facilitating HCV transmission [252]. Ulcerative STIs, including syphilis, LGV, and Herpes are common among HIV-infected MSM and may also

increase risk of HCV [253, 254]. Certain sexual practices may place some MSM at risk for sexual transmission of typically blood–borne pathogens. Group sex, receptive fisting, use of sex toys, and enema use before anal sex may induce mucosal trauma facilitating HCV transmission [255, 256]. Sexualized drug use is associated with HCV transmission in HIV-infected MSM and may result in higher rates of condomless sex, greater numbers of sex partners, and anal/rectal trauma resulting from longer and more intense sexual encounters while under the influence of drugs [257, 258]. Because HCV RNA is more frequently found in the semen of HCV/HIV coinfected versus HCV monoinfected persons, the practice of serosorting (HIV-infected men choosing other HIV-infected men as sex partners) may also facilitate higher rates of HCV transmission among HIV-infected MSM [259].

Most often, acute HCV infection is asymptomatic. When present, symptoms are indistinguishable from those caused by HAV and HBV. Unlike HAV and HBV acquired in adolescence and adulthood, HCV more often causes chronic infection, cirrhosis, and hepatocellular carcinoma. The natural history of HCV is influenced by coinfection with HIV, resulting in more severe clinical disease in dual-infected persons. Clinical manifestations of acute HCV may differ [260]. Further, HIV infection may accelerate liver fibrosis in chronic HCV infection [261].

HCV screening is recommended for one-time testing in MSM born between 1945 and 1965 [262]. MSM with risk factors for HCV infection including IDU should be screened periodically according to active risk [263]. HIV-infected MSM should be screened annually for HCV infection (see Table 11.2). Anti-HCV antibody tests should be used for screening. When positive, confirmatory testing by nucleic acid amplification evaluating for viremia confirms chronic infection [263]. In persons with low CD4+ T cell counts, false negative anti-HCV results may be observed. In such cases where clinical suspicion is high, nucleic acid amplification should be performed [65]. Patients with HCV should be evaluated for treatment [264]. Prophylactic vaccines are not available for the prevention of HCV. Prevention is mediated by risk reduction in vulnerable populations. Highly active treatment is available for Hepatitis C and all persons with Hepatitis C should be evaluated for treatment.

Conclusions

MSM are at high risk for STI. Healthcare providers caring for HIV-infected MSM should maintain an open dialogue with their patients regarding potential exposures to STI, vaccinate, and screen when appropriate. For MSM presenting with symptoms concerning for STI syndromes, treatment should be offered while awaiting diagnostic tests. Furthermore, when treatment is unsuccessful, the provider should explore sexual behavior to identify causes of symptoms other than STI.

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Transgender Individuals

12

Tonia Poteat and Asa E. Radix

Introduction

Transgender is an umbrella term used to describe a diverse array of individuals whose gender identity and/or presentation differs from the sex they were assigned on their original birth certificate. Transgender people vary in whether they modify their bodies to align with their gender. Some people make no anatomical changes while others undergo hormone therapy, surgical interventions, and/or other treatments to feminize or masculinize their anatomy. In addition to physical diversity, gender identities are dynamic; and the terms transgender people use to describe themselves are changing and growing. Gender identity differs from sexual orientation, and transgender people may have sexual partners of any gender. Figure 12.1 provides a simplified depiction of the spectrum of gender and sexual orientation.

This natural evolution in self-identities and diversity in anatomy make transgender health a dynamic field. It also poses challenges in the collection of epidemiologic data among transgender populations. There is no sampling frame for all transgender people, therefore probability sampling is difficult and most studies use convenience samples. A review of the health literature finds no consistent inclusion or exclusion criteria for transgender study participants [1], and it is often unclear how study participants were recruited or identified. Clinical studies among transgender people are often limited by small sample sizes as well as lack of clarity about the hormonal and surgical histories that may impact STI risk and outcomes. Despite these limitations, there are growing data to suggest that transgender people, particularly transgender women, experience a heavy burden of STIs. Given the social stigma that many transgender people experience as well as the breadth of transgender identities and anatomies, medical providers will benefit from specific knowledge and approaches to STI prevention and treatment among transgender people.

Epidemiology

Transgender women bear a disproportionate burden of HIV with a worldwide prevalence of 19% and 49 times the odds of infection compared to the general population of reproductive age adults [2]. Annual HIV incidence as high as 3.3 per 100 person-years has been reported among

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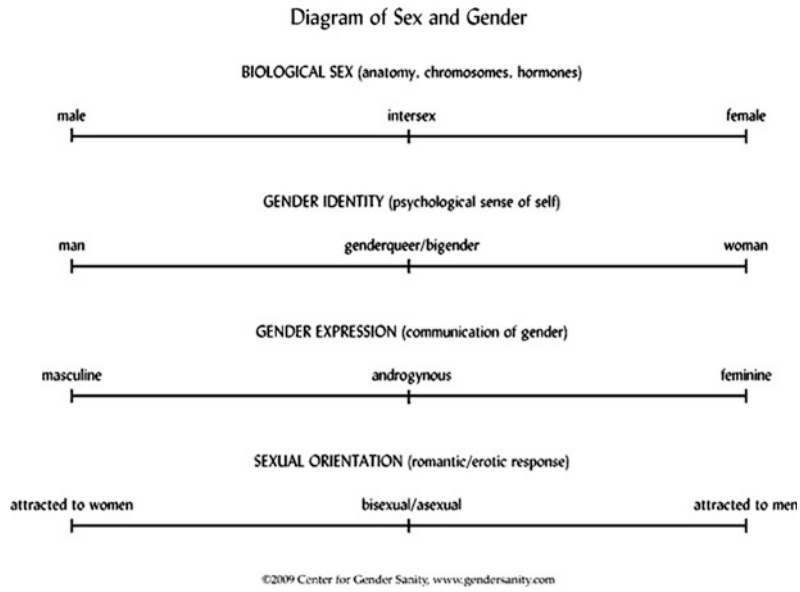


Fig. 12.1 Diagram of sex and gender. Reprinted with permission from the Center for Gender Sanity www.gendersanity.com

transgender women in the United States [3] and as high as 10.7, globally [4]. Research on HIV among transgender men is very limited [5–8]. Available data have found HIV prevalence as low as 0% at HIV testing sites [7] to as high as 10% in an STI clinic sample [8].

Data on STIs among transgender men are even more limited and only available from U.S.-based studies. A recent community clinic sample of 23 transgender men found that 8.7% had a history of one or more laboratory-confirmed STIs [6]. In a sample of 69 transgender men drawn from an STI clinic, participants had been diagnosed with a range of STIs including anal, urogenital, and pharyngeal infections with GC (4.4, 2.9, 8.7%) or CT (4.4, 4.4, 1.5%), respectively, as well as syphilis (1.5%) over the preceding 12 months [8]. Data among 223 transgender women from the same STI clinic found similar rates of infection with anal, urogenital, and pharyngeal GC (6.5, 1.8, 9%) and syphilis (1.8%). Prevalence of pharyngeal (4.9%) CT was higher while anal (2.7%) and urogenital (0%) CT was lower among transgender women, compared to transgender men in the clinic [8]. A prospective cohort study of transgender women found high incidence of STIs in the first year, with rates of 4.2, 4.5, 3.6, and 2.4% for GC, CT, syphilis, and hepatitis B, respectively [3].

Comparative studies typically find higher prevalence of STIs among transgender women compared to other populations. For example, a study of syphilis among sex workers in India found a syphilis prevalence of 13% among transgender women sex workers compared to 0.3% among male sex workers, and 6.6% among non-transgender female sex workers [9]. In a study of sex workers in Argentina, transgender women sex workers demonstrated an HBV prevalence of 40% compared to 22% among male sex workers [4].

Such high prevalence of STIs has not been limited to studies of transgender sex workers. A clinic-based study in India found syphilis prevalence to be 12.5% among transgender women, compared to 5.9% among all clinic attendees [10]. In a probability sample of transgender women in Peru, prevalence of syphilis was 22.9% and HSV-2 was 79.4% [11]. In a medical record review of 284 transgender women seeking genital reconstruction surgery in Brazil, 51% had a history of an STI [12]. History of an STI diagnosis was the strongest predictor of HIV infection (OR 6.6, 95% CI: 3.25–11.97),

stronger than a history of sex work (OR 2.74, 95% CI: 1.42–5.27).

There are small but emerging data on anogenital warts and HPV among transgender women. A study of transgender sex workers in Argentina found HPV-DNA in 111/114 participants (97.4%) using self-collected anal cytobrush samples [4]. A study of 84 hijra in India found that 10% had genital warts on exam [13]. Brown et al. [14] found visible anogenital warts in 21/96 (22%) transgender women during baseline examination for a cohort study in Peru. Of participants with warts, 15/21 (71%) had only anal warts [15]. Interestingly, another study of transgender women in Thailand found self-reported penile warts to be significantly associated with HIV (OR 4.71, 95% CI: 1.29–17.25); however self-reported anal warts was not associated with HIV (OR 1.42, 95% CI: 0.56–3.59) [16]. It is possible that the presence of penile warts was a marker for sexual role versatility, which was significantly associated with HIV infection compared to only receptive role in a multivariable model (OR 2.35, 95% CI: 1.11–4.98).

Basic Science

Laboratory studies of STI pathogenesis among transgender patients are lacking. However, the effect of sex hormones on immune regulation and pathogen susceptibility in the reproductive tract may have implications for transgender patients using hormone therapy. Estradiol and progesterone have been shown to regulate immune function in the vagina, cervix, uterus, and Fallopian tubes in ways that impact susceptibility to bacterial and viral pathogens [17, 18]. Declines in estradiol, induced by exogenous testosterone, result in vaginal atrophy and thinning of the epithelium [19, 20], creating conditions that may increase susceptibility to HIV and STIs. There are few studies of sex hormone effects on the anus and rectum [21–23], and even fewer assessing immune function of the cisgender male reproductive tract [24].

Pertinent Clinical Issues Unique to This Population

Gender Affirmation

Gender affirmation refers to the process by which someone receives social recognition and support for their gender. Experiences of stigma, discrimination, and violence related to gender identity and expression have been well documented among transgender people [25]. The Model of Gender Affirmation links transgender-specific stigma to heightened risk for HIV and STIs among transgender women [26], and has been applied to sexual risk among transgender men who have sex with non-transgender males [27]. The Model posits that anti-transgender stigma (e.g., family rejection) leads to both decreased access to (e.g., lack of financial support) and increased need for gender affirmation. Transgender people may seek to meet this need for affirmation through behaviors (e.g., sex work that provides income and affirms gender) that increase their risk for HIV and STIs. When providing sexual health services for transgender patients, it is important for healthcare providers to keep in mind the social context that leads to the high prevalence of STIs.

Access to Sexual Health Services

Several studies have demonstrated that transgender people avoid both preventive and urgent medical care [25, 28–31]. Some of the reasons stated have been discomfort with providers [31, 32], having to teach providers about transgender health [32], discomfort with physical exams [31], discrimination by healthcare workers [25, 30, 33, 34], harassment from other patients [30], lack of providers knowledge about transgender health issues [25, 33], and fear of disclosing their transgender identity [34]. On the other hand, engagement in care is enhanced by providing gender affirming services and improving provider knowledge so that they can competently care for

transgender clients as well as be respectful of their clients' gender identity [35]. Unfortunately, many providers are not knowledgeable about transgender health issues, since most have not had adequate training on this topic [36]. There are several steps that can be taken to improve provider–patient interactions that will increase the likelihood that transgender individuals will engage in preventive care and undergo STI screening.

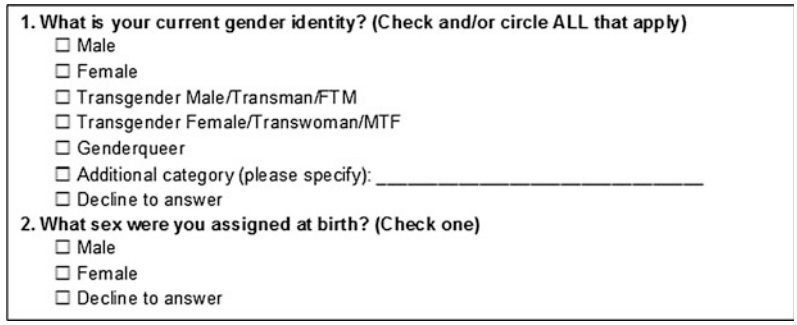
Provider–Patient Interaction and Affirming Language

Creating a welcoming and transgender-inclusive environment involves every person in the healthcare setting. It is important that healthcare workers are trained not to make assumptions about gender identity and that they use gender-neutral forms of address, e.g., avoid saying "sir" or "ma'am." Registration forms should be provided that allow people to appropriately self-identify their gender. The best practice for determining gender identity is considered to be a two-step system that asks about sex assigned at birth as well as current gender identity as noted in Fig. 12.2 [37, 38]. Healthcare staff should use the patient's preferred name and pronoun during patient interactions, regardless of the legal or insurance name and gender marker. Medical providers should be given training about the specific healthcare needs of transgender clients, especially in terms of preventive care and transgender-specific treatment.

Many transgender patients may be uncomfortable talking about their sexual history, sex partners, or sexual practices. Building rapport may take longer than with non-transgender patients due to past experiences or expectations of healthcare discrimination. When talking with patients about their anatomy it is recommended that medical providers ask about and use the terms that patients themselves use to describe their body parts [39]. An example would be a transgender man who may use the term "front hole" for "vagina." Understanding and mirroring terms when talking to patients and maintaining open communication using respectful language, including appropriate use of preferred names and pronouns, are strategies that will allow medical providers to put patients at ease and obtain accurate information on sexual health and STI risk (Table 12.1).

Anatomic Considerations

Some transgender clients undergo gender confirming genital surgery that may impact their sexual practices and needs for screening. It is important that medical providers understand the scope of surgeries available and resultant anatomical changes. A transgender man may undergo genital surgeries such as phalloplasty (creation of a phallus using skin from the forearm, chest wall or thigh) or metoidioplasty (separation of the clitoris from the labia minora). These surgeries may occur alone or in


1. What is your current gender identity? (Check and/or circle ALL that apply)
- ☐ Male
- ☐ Female
- ☐ Transgender Male/Transman/FTM
- ☐ Transgender Female/Transwoman/MTF
- ☐ Genderqueer
- ☐ Additional category (please specify): _____
- ☐ Decline to answer

2. What sex were you assigned at birth? (Check one)
- ☐ Male
- ☐ Female
- ☐ Decline to answer

Fig. 12.2 Collection of gender identity on a patient intake form. Adapted from the University of California San Francisco, Center of Excellence for Transgender Health

Table 12.1 Best practices for working with transgender patients

Create registration forms that allow transgender patients to identify
Avoid gendered language when addressing patients (e.g., Ma'am, Sir)
Ask patients what name and pronoun they prefer to use
Avoid assumptions about sexual orientation or behavior
Discuss choice of language to describe anatomy
Avoid describing patients as "pre-op" or "post-op"
If you make a mistake (e.g., use the wrong pronoun) apologize

combination with vaginectomy or colpoclesis (removal of the vagina). Understanding the extent of surgeries will allow providers to know what anatomic sites need to be examined or screened. For transgender women, some may undergo orchiectomy alone, or also have vaginoplasty (Fig. 12.3), or creation of a neovagina using either inverted penile skin (penile inversion) or a loop of sigmoid colon (colovaginoplasty). There have been no published reports of urethral STIs affecting transgender men who have undergone phalloplasty. There have been several case reports of STIs (genital warts, bacterial vaginosis, and gonorrhea) among transgender women who have undergone vaginoplasty [40–44].

Sexual History Taking

The CDC recommends the "Five P's" approach to obtaining a sexual history, documenting responses in five key areas: partners, prevention of pregnancy, protection from STIs, practices, and past history of STIs [45]. These tools, however, may be inadequate to address transgender individuals, who may have different ways to describe themselves, their anatomy and their sex partners, regardless of gender affirming therapies undertaken.

Partners of transgender people may be male, female, or intersex, including transgender and non-transgender people [46–49]; therefore, questions about sexual partners need to be

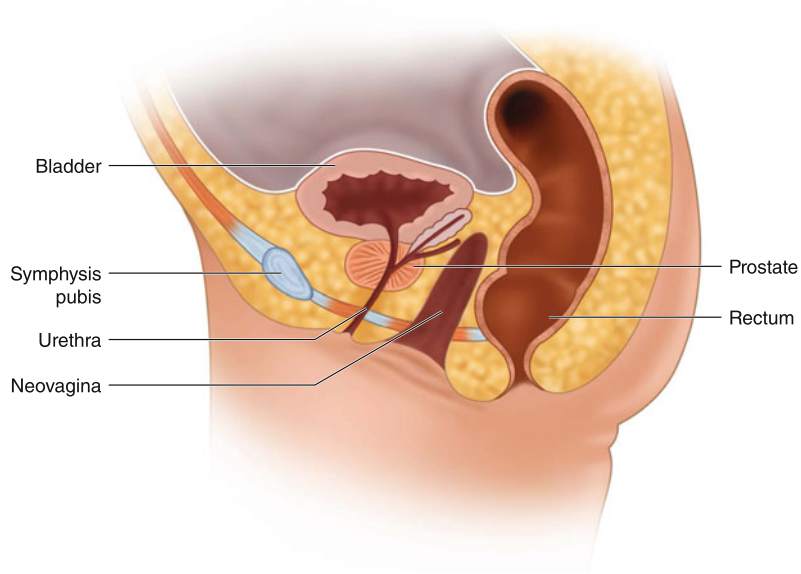


Fig. 12.3 Transgender female anatomy after vaginoplasty

Table 12.2 Gender inclusive, non-traumatizing language for genital exams[a]

Gendered	Less gendered
Vulva Penis, testicles	External pelvic area Outer parts
Labia or "lips"	Outer folds
Vagina	Genital opening, frontal opening, internal canal
Uterus, ovaries Prostate	Internal organs Internal parts
Breasts[b]	Chest
Pap smear, prostate exam	Cancer screening, HPV screening
Bra/panties/briefs	Underwear
Pads/Tampons	Absorbent product
Period/menstruation	Bleeding
Negative connotation	Neutral or positive connotation
Stirrups	Footrests
"Open your legs"	"Let your legs drop to either side"
"Blades" of the speculum	"Bills" of the speculum or "Opening the speculum"
"You're going to feel a pinch"	"You may feel pressure"

[a]Adapted from [51]
[b]Transgender women may prefer "breast"

inclusive of transgender partners. Pregnancy considerations are important to discuss as transgender men on testosterone are still susceptible to pregnancy, if they have sex with non-transgender men (or fertile transgender women), [50] and may need to be counseled on contraceptive options. Some transgender men start having sex with non-transgender men after initiation of testosterone, and some populations of gay-identified transgender men have been shown to have inconsistent knowledge about sexual risk [46]. "Protection for STIs and Practices" will require an understanding of the person's current anatomy, therefore, medical providers should inquire about any genital surgeries that have been undertaken. Normalizing the conversation and being knowledgeable about surgical options may help to put the patient at ease. For example, "Some transgender men have had gender affirming (bottom) surgeries. Have you had any surgeries, such as metoidioplasty (meta) or phalloplasty (phallo)?" If yes, the provider should determine if the vagina and/or cervix were retained. Another example would be, "Some transgender women have had gender affirming (bottom) surgeries. Have you had any surgeries like orchiectomy (orchi) or vaginoplasty?" Sexual practices may also need to explained in different terms, e.g., "Do you have front sex?" instead of "vaginal sex." Potter and colleagues have published guidelines for gender-neutral and non-traumatizing language for use during genital exams with transgender men [51]. Table 12.2 has been adapted from these recommendations.

Screening and Diagnostic Recommendations

Prior to gender affirming genital surgery, transgender women may engage in anal receptive and/or insertive sex, and transgender men may engage in vaginal and anal sex; however, there are limited data on behavioral practices or risks after undergoing genital reconstruction [52–54]. Although transgender people are included as a special population in the 2015 CDC STD treatment guidelines [45], there are currently no standards of care that address the frequency and

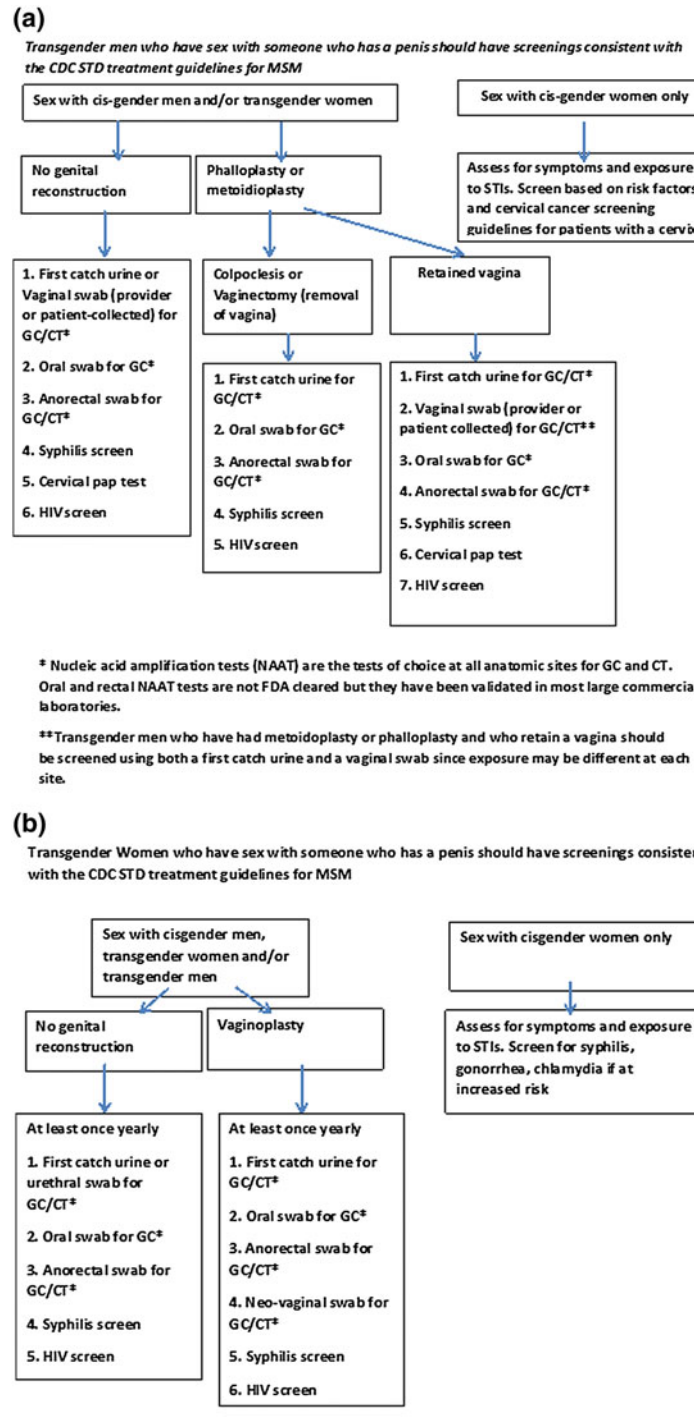


Fig. 12.4 **a** Screening for sexually transmitted infections in transgender men. **b** Screening for sexually transmitted infections in transgender women

type of screening for transgender women or men who have undergone these surgeries.

In general, screening should be undertaken based on an understanding of sexual partners, current anatomy, and sexual practices (Fig. 12.4 a, b). For transgender women and transgender men who have sex with partners who have a penis, it is reasonable to suggest at least annual screening for STIs, including HIV, syphilis, gonorrhea and chlamydia, with sites of testing based on current anatomy and areas potentially exposed. For transgender men and transgender women who have sex only with non-transgender women, it is likely that STI risk is lower, though a detailed sexual health history should be performed with appropriate STI testing as indicated. Specific attention should be made to screening of the neovagina with annual inspection for genital warts and lesions. If there are symptoms (itching, discharge, pain) then testing should be performed for gonorrhea and chlamydia and other STIs based on physical exam findings (i.e., genital herpes, syphilis if ulcers and/or rash).

Unique Treatment Considerations

Drug Interactions

It is important to do a thorough review of current medications, including medications used for feminization or masculinization, before prescribing treatment. The list of medications should include not only those prescribed for the patient but also any medications or herbal products the patient is getting from friends, over-the-counter, or other non-medical sources. Transgender patients may supplement their prescribed dosage of hormone therapy with additional medications, so it is important to ask about alternative sources even among patients in care. Significant drug–drug interactions are uncommon but may exist between oral estrogens and medications metabolized via the cytochrome P450 pathway. In the case of HIV medications, amprenavir and fosamprenavir are the only antiretroviral medications contraindicated to be co-administered with estradiol due to risk of virologic failure [55]. Where there are interactions between antiretroviral agents and estrogens, it is typically the serum concentration of estrogen that is lowered rather than the antiretroviral drug.

Soft Tissue Fillers

Soft tissue fillers, such as loose silicone, may be injected to feminize the appearance of the hips, buttocks, breasts, cheeks, and/or lips [56, 57]. Potential adverse effects include inflammatory reactions, migration of silicone or other fillers throughout the body, and hardening of the substance once under the skin. The presence of hardened silicone in the buttocks may require selection of an alternative site for administration of intramuscular injections for the treatment syphilis or other STIs.

Conclusion: Summary and Take-Home Messages

Sexual health services, including STI treatment, for transgender patients are best provided in a gender-inclusive, trauma-informed manner where no assumptions are made about a patient's identity, partners, sexual behaviors, or anatomy. Preferred names and pronouns should be used in all patient communications. The sexual history and screening exam should be appropriate for the patient's anatomy, the anatomy of their sexual partner(s), and the types of sexual activities in which they engage. Providing welcoming and informed STI care for transgender patients can be a rewarding way to improve their health and counter the stigma that so often leads to delay or avoidance of care.

Case Illustration

"Monica" is a 36-year-old African-American transgender woman who was diagnosed with HIV during a routine screening in 2009. For

several years after her diagnosis, she was not fully engaged in HIV care, receiving intermittent care from various providers. In 2014, she found a healthcare provider with whom she felt comfortable and agreed to start antiretroviral therapy (ART) with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild). At the time of ART initiation, her HIV RNA PCR (viral load) was 214,000 copies, and her CD4 count was 196. She tolerated this regimen well and has remained virally suppressed for several years with a current viral load <20 copies. Her CD4 count increased over time and has remained between 450 and 550 over the past year. Monica is otherwise healthy and has no other chronic illnesses and has had no surgeries. In addition to Stribild, she takes estradiol valerate 20 mg intramuscularly (IM) every week as well as 100 mg of oral spironolactone daily for gender affirmation.

Clinical Presentation

Monica presented to the office for her routine HIV follow-up visit. During the review of systems, she reported that since her last visit, she noticed small bald patches where her hair had started falling out. However, she had seen a dermatologist who gave her a topical medication, and the patches were improving. She denied any rash or other skin condition.

Sexual History (Modified from CDC 5 P's)

Partners

Her first sexual encounter was at the age of 15 years. The number of sexual partners in the previous 12 months was approximately 20. In the past 2 months, she has had two sexual partners. All of her partners were non-transgender men. Her last sexual encounter was 5 days ago. Monica stated that it was hard to meet a good man and that "men just want one thing, then they move on."

Practices

She reported that she prefers to be the receptive partner or "bottom" during anal sex, but sometimes a partner will convince her to be the insertive partner. She also performs oral sex and manual stimulation of her partners.

Prevention of Pregnancy

She denies any non-transgender female partners or partners who were transgender men.

Protection from STIs

She always tries to use condoms, but admits that sometimes she has sex without a condom when she's been drinking. She stated that she always tries to douche before and after sex to "keep herself clean," practices she learned from older mentors in the transgender community.

Past History of STIs

She has been treated for anal gonorrhea three times in the past 6 years, the last time being 6 months ago; she was also treated for chlamydia at that time. She denies a history of any other STIs. She has been screened annually for syphilis since receiving HIV care: all have been negative. Her most recent STI screening was 3 months ago.

Physical Exam

Her vital signs were normal and her physical exam unremarkable except for notable patches of thin hair on the right area of her scalp, near the hairline. Her anal and genital exams were unremarkable, with no sign of bleeding, lesions, or discharge, and no anal masses or inguinal lymphadenopathy.

Initial Management

A full STI screen was conducted, including a reflex RPR, NAAT for gonorrhea (GC) and chlamydia (CT) in the urine as well as oropharyngeal and rectal swabs. Monica was engaged in a discussion about safer sex practices, condom

use and negotiation. The healthcare provider also broached the topic of douching. The patient was educated about the health implications of these practices, including the risk that douching will increase susceptibility to infection because it causes inflammation of, or damage to, the mucous membranes. At this point in the discussion, the patient also disclosed that she had trouble keeping a job when her gender identity was discovered, and she sometimes sold sex to get extra money to pay for her hormone therapy which was not covered by her insurance plan. She was referred to case management for assistance with paying for medication and linkage to job training programs. She was also engaged in a client-centered counseling session to address barriers to condom use.

Management and Clinical Course

A few days later, her laboratory results became available. The RPR titer was 1:64 and the reflex fluorescent treponemal antibody absorbed test (FTA-ABS) was positive. The oral GC test was positive. All other tests for gonorrhea and chlamydia were negative. The patient was contacted upon receipt of the laboratory test results and asked to return to the clinic. During her clinic visit, she was diagnosed with secondary syphilis based on her hair loss and positive RPR as well as oral gonorrhea. She received the following treatment: benzathine penicillin G 2.4 million units IM in a single dose, as well as ceftriaxone 250 mg IM in a single dose, and azithromycin 1 g orally in a single dose. It was also recommended that she refer her sexual partners for treatment; and she was informed that the health department would work with her to contact her partners in a confidential manner. A follow-up appointment was made for 3 months later.

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STIs Among Women Who Have Sex with Women

13

Linda Gorgos and Jeanne Marrazzo

Introduction

Recent data indicate that same-sex behavior among women in the United States is not uncommon. The National Survey of Family Growth 2002, a nationally representative sample of households in the United States, reported that 4.4% of women aged 15–44 years old had a female sex partner in the past 12 months, and 1.3% reported having exclusively female sex partners in the past 12 months. These investigators used measures of self-reported sexual identity and sexual behavior to estimate that 1.3–1.9% of US women self-identify as lesbians, and that 3.1–4.8% are bisexual [1]. In large population-based surveys, lifetime same-sex behavior is commonly reported by women, including 12% of women in the 2006–2008 National Survey of Family Growth (NSFG), 9.7% of women in the 1999–2001 British National Survey of Sexual Attitudes and Lifestyles [3], and 7.1% of women in National Health and Nutrition Examination Surveys (NHANES) 2001–2006 [2–4]. Despite these substantial numbers, the evidence based on sexual risk, epidemiology and natural history of sexually transmitted infections (STI) and related health care delivery among WSW is very limited. We review here the available evidence for key STI in WSW, and emphasize important preventive measures that all healthcare providers should be aware of for this understudied group of women.

Basic Science Concepts

The use of molecular testing methods, such as nucleic acid amplification assays, for detection of STIs, including chlamydia, gonorrhea, and HPV, has expanded the ability to detect infection and further define the epidemiology of STI among women in general. New data utilizing molecular testing methods more fully describe STI among populations of WSW at a local, regional, and national level [5–8].

Bacterial vaginosis (BV) is a common vaginal infection that tends to be more common among women with female sex partners [9]. With the advent of 16S ribosomal RNA gene polymerase chain reaction and pyrosequencing to define the bacterial communities involved in BV, there has been a greater appreciation of the microbial diversity and complex nature of this condition [10–14]. These methods can identify previously uncultivable or difficult to culture microorganisms, and this has

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allowed a more detailed understanding of specific vaginal flora associated with prevalent BV infection [15], incident BV infection [16], persistent BV following treatment [17], potential extra-genital reservoirs of vaginal bacteria that may contribute to new BV infection [18], and vaginal bacteria shared between female partners [19]. Many of these studies have included WSW in part or exclusively. Moreover, efforts using molecular methods to fingerprint specific strains of *Lactobacillus* bacteria in female sex partners strongly suggest that such partners share these specific strains, and the likelihood of their doing so is directly related to the duration of their sexual partnership [19]. While the etiology and pathogenesis of BV is not completely understood, these data have contributed to an expanded understanding of BV and the ongoing investigation of whether BV can be sexually transmitted between same-sex and opposite-sex partnerships in women.

Case Illustration

A 22-year-old college student presented to her university health service complaining of vaginal discharge and odor for 2 weeks that had not responded to over-the-counter vaginal clotrimazole cream. She reported having a female sex partner for the past 6 months. She was prescribed metronidazole 500 mg orally twice daily for 7 days for presumptive treatment of bacterial vaginosis, and a pelvic exam was not performed at the initial visit. She noted some improvement with metronidazole but at 2 weeks post-treatment continued to experience vaginal discharge with new onset of inter-menstrual bleeding and abdominal pain. On reevaluation a urine pregnancy test was negative. Pelvic exam disclosed mucopurulent discharge from the cervix and cervical motion tenderness. A vaginal wet mount showed no evidence of vaginal candidiasis, trichomoniasis, or BV. She was started on treatment for pelvic inflammatory disease (PID). A cervical swab sent for nucleic acid amplification testing returned positive for *Chlamydia trachomatis* and negative for *Neisseria gonorrhoeae*. She responded rapidly to treatment for PID. On further interview she reported a history of two prior male sex partners and one prior female sex partner in her lifetime. Her current partner was asymptomatic and had not been recently tested for chlamydia.

Epidemiology

A major challenge in interpreting the studies examining sexual risk behaviors and STI among WSW results from the fact that different studies often use different methods to categorize and define sexual contact between women. Some studies have identified these women based on self-identified sexual orientation ("homosexual," "lesbian," "bisexual," "heterosexual"), while others use reported sexual behaviors and same-sex partner selection over time (history of a female partner during the lifetime, or during a more recent period, such as the past year; history of male partners) alone or in combination with measures of sexual orientation. This limits the methodological comparability across studies, and should be considered in interpreting the available evidence. For data discussed below, the definition of WSW used in the particular study will be included for reference.

Women who have sex with women are a diverse group with variations in sexual identity, sexual behaviors, sexual practices, and risk behaviors. Sexual identity is not necessarily in concordance with sexual behaviors and gender of sexual partners [3, 4, 20–22]. Past and current studies affirm that the majority of women (up to 87%) who report same-sex behavior have had male partners in the past and may continue to do so in the present (6–23%) [23–25]. It cannot be presumed that women who identify as "lesbian" do not or have not had male partners. Surveys among adolescent and young women also highlight the potential discordance between sexual identity and gender of partner(s). Among women aged 15–44 self-identifying as heterosexual in the 2006–2010 National Survey of Family Growth (NSFG), a national population-based household survey, 11.2% reported ever having a same-sex partner, and 1.8% reported a female sex partner in the past year [20]. Girls in 8th to

12th grade participating in the Youth Risk Behavior Survey (YRBS) for 2005 and 2007 who self-identified as lesbian reported having male only partners (25%), female only partners (34%), and both male and female partners (40%). For girls who reported both male and female partners, 28% self-identified as heterosexual, 7% as lesbian, and 58% as bisexual [26].

Some women who have both female and male partners (WSWM) may also evidence increased risk-taking behaviors compared to their peers with exclusively opposite-sex (WSM) or exclusively same-sex partners. Prior surveys included women attending STD clinics, primary care settings, or living in specific regions. Women who reported a past or current history of both male and female partners were more likely to report high-risk behaviors including: exchanging sex for money or drugs [27], having partners who were injection drug users [24, 27, 28], sex with MSM or bisexual men [24, 27, 28], an HIV positive partner [27], and both past and current drug use [28]. While reporting having "riskier" male partners, the lesbian and bisexual women were more likely to engage in protective behaviors such as condom use and to recognize their risk of STI and HIV with subsequent care seeking for testing [24].

Population-based surveys of women living in the US, UK, and France reported potential for increased sexual risk among WSWM compared to women with exclusively same-sex or opposite-sex partners including: a higher number of male partners [3, 7, 20, 22]; high alcohol intake or binge drinking [3, 20, 22]; drug use [3, 20, 22]; and partner concurrency [7, 20, 22]. Similar patterns were seen among adolescents and young women participating in YRBS and NSFG surveys, Those who identified as "other than heterosexual" or who reported same sex partners reported: more recent and lifetime partners [26, 29, 30]; illegal drug use [26, 29]; being coerced into sexual contact [29, 30]; and a younger age of heterosexual sexual debut [30]. In summary, many early studies of risk behaviors among WSW were based on convenience samples or on women attending STD clinics and are not necessarily generalizable to all women who have sex with women. However, it does appear that some WSW, particularly adolescents and young women as well as some women with both male and female partners may be at increased risk for STI and HIV based on reported risk behaviors.

Few data are available on the risk of STI conferred by sex between women, but transmission risk probably varies by the specific STI and sexual practice (e.g., oral–genital sex; vaginal or anal sex using hands, fingers, or penetrative sex items; oral–anal sex; and genital–genital contact). Practices involving digital-vaginal or digital-anal contact, particularly with shared penetrative sex items, present a possible means for transmission of infected cervicovaginal secretions. Transmission of human papillomavirus (HPV) can occur with skin-to-skin or skin-to-mucosa contact, which can occur during sex between women. A recent small study also documented the presence of HPV on vaginally inserted sex toys both before and after cleaning which could provide a mechanism for transmission of HPV between partners using shared sex toys [31].

Until recently, few published data on the risk of bacterial STI in WSW were available, and infections with major pathogens of concern, including *C. trachomatis* and *N. gonorrhoeae*, were considered to be uncommon. Earlier studies that included women from STD clinics and sexual health centers reported a prevalence of chlamydial infection among WSW ranging from 0.6 to 3.0% and of gonorrhea from 0.3 to 2.8% [32–35]. However, no data on chlamydia or gonorrhea infections in WSW from community or population-based venues were available. In 2008, Singh et al. examined chlamydia positivity among WSW aged 15–24 years old tested at family planning clinics participating in the Infertility Prevention Project in the Northwestern U.S. from 1997 to 2005 [6]. Women reporting sex with women (WSW) and women reporting sex with both men and women (WSMW) in the 12 months prior to testing were included. Chlamydia positivity was 7.1% among both WSW and WSMW and remained stable over the period of observation in the study. Chlamydia positivity for women reporting only

male partners in the 12 months prior to testing was 5.3%. Risks for chlamydia among WSW and WSMW were age <20 years, non-White race/ethnicity, new sex partner, symptomatic sex partner, symptoms, exposure to chlamydia, and cervicitis, and did not differ from those traditionally identified among women who report sex only with men.

Recent studies have examined STI prevalence and risk behaviors among diverse populations of WSW, including international settings and African American WSW. Convenience samples of WSW living in China demonstrated a relatively high prevalence of bacterial STI compared to prior surveys (gonorrhea 16%, chlamydia 4%) [36]. Testing among African American WSW attending an urban STD clinic included women with exclusively female partners in the past year and women with both male and female partners in the past year. STI at the time of visit were common overall in these women: *Trichomonas vaginalis* (TV) in 18.3%, *C. trachomatis* (CT) in 11%, *Mycoplasma genitalium* (MG) in 7.6%, *N. gonorrhoeae* (NG) in 3.7%. WSWM were more likely to be diagnosed with a current STI versus WSW: TV (25.0% vs. 13.5%); CT (22.5% vs. 2.7%); NG (7.5% vs. 0.9%); any STI (47.5% vs. 18.3%) [5].

Other sexually transmitted infections can be passed between female partners, including trichomoniasis [37, 38], syphilis [39], and hepatitis A [40]. Although it is presumably rare, sexual transmission of HIV may also occur in this manner [41]. Prior data suggesting potential HIV transmission between female partners is based on case reports where presumed female–female transmission was based on a lack of other identified risk factors [42–46]. Two case reports identified women who had no other reported behavioral risk for HIV acquisition other than sexual contact with a single HIV-infected female partner. Female–female sexual transmission was supported by recent infection with a similar HIV genotype to the known HIV-infected female partner in one case [41]. In the other case, transmission occurred in the context of an HIV discordant monogamous same-sex partnership where no risk factors for transmission were identified other than sexual contact. The virus infecting the two women had $\geq$98% sequence identity in three genes by phylogenetic linkage analysis [47]. More common is the potential for WSW to acquire HIV through other modes, including injection drug use and sexual contact with high-risk male partners [27, 48, 49].

Data are most extensive for the incidence and risk of some viral STI among WSW, particularly herpes simplex type 1 and 2 (HSV-1 and HSV-2) and human papillomavirus (HPV). The 2002 National Survey of Family Growth provided information on self-reported viral STI among women aged 15–44 years old. A history of "genital herpes" or "genital warts" was reported more frequently by bisexual women (15.0–17.2%) than by lesbians (2.3–6.7%) and their heterosexual counterparts (8.7–10.0%) [25].

A seroprevalence study of HSV in 392 WSW found that 46% had antibodies to HSV-1 and 8% had antibodies to HSV-2. Increasing age was predictive of higher seroprevalence of both HSV-1 and 2, and HSV-2 seropositivity was associated with having a male partner with genital herpes. Of the 78 women in the study reporting never having had a male partner, 3% were HSV-2 seropositive. HSV-1 seroprevalence increased with increasing numbers of female partners [50]. In a separate study of HSV-1 prevalence and acquisition among young women, receptive oral sex was associated with HSV-1 acquisition [51]. More recent data from NHANES conducted in years 2001–2006 among women aged 18–59 demonstrated an HSV-2 seroprevalence of 30.3% among women reporting same sex partners in the past year, 36.2% among women reporting same sex partners in their lifetime, and 23.8% among women reporting no lifetime same sex behavior [2]. HSV-2 seroprevalence among women self-identifying as "homosexual or lesbian" was 8.2%, similar to a prior clinic-based study of WSW.

While genital human papillomavirus infection is common, with certain HPV types associated with cervical cancer, WSW were once presumed to be at "low risk" for HPV acquisition and cervical cancer. Data now strongly support that HPV infections are common among WSW and that sexual transmission of HPV almost certainly

occurs between women [52–54]. Prior case reports highlighted the presence of cervical neoplasia and HPV among women who had no history of sex with men [55, 56]. HPV in WSW has been studied using both HPV serology and DNA detection methods. In a 1995 study, among WSW who reported never having had a male sexual partner, 26% had antibodies to HPV-16 and 42% had antibodies to HPV-6. No difference in the prevalence of HPV-16 and HPV-6 antibodies was found between those women with and without a history of male partners. HPV DNA was detected in genital tract specimens in 30% of the women enrolled, and the prevalence of squamous intraepithelial lesions (SIL) on Pap smear was 4%, similar to that found in heterosexual women [52]. A subsequent larger study again showed the high prevalence of HPV in WSW, with 13% having HPV DNA in genital tract specimens (74% of which were oncogenic types) and 4.4% having either low or high grade SIL [53]. A large cohort of HIV seropositive and HIV seronegative women in the US have been followed longitudinally as part of the Women's Interagency HIV Study with Pap and HPV DNA PCR tests obtained every 6 months. Women reporting no male and at least one female sex partner in the past 5 years (WSW) were matched to women reporting sex only with men (WSM). Pap abnormalities and HPV were common at study entry, even among the HIV seronegative WSW with a remote history of last male partner (>5 years): abnormal Pap (9% vs. 11%), any HPV DNA detected (27% vs. 20%), carcinogenic HPV (4.6% vs. 8.5%) [8].

Despite these persuasive data, WSW from diverse settings, particularly those with a history of having only female partners, are less likely to report having had Pap smear screening and too frequently believed they had less need for cervical cancer screening [52–54, 57–61]. Women identifying as lesbian or bisexual have also reported lower coverage for HPV vaccination [62, 63]. HPV vaccine uptake among girls aged 13–17 years in the National Immunization Survey-Teen (NIS-Teen) 2012 estimated that 53% of girls received at least one dose (vaccine initiation) and only 33% completed the three dose vaccine series as of 2012 [64]. Estimated vaccine coverage is even lower among young adults with estimates of HPV vaccine initiation among women aged 18–26 ranging from 23 to 45% [65, 66]. Utilizing NSFG 2006–2010 data for 15- to 25-year-old women asked about HPV vaccination, vaccine awareness was similar among heterosexual, bisexual, and lesbian participants. However, only 8.5% ($p = 0.007$) of lesbians and 33.2% ($p = 0.33$) of bisexual women who had heard of the vaccine had initiated vaccination compared with 28.4% of their heterosexual peers [63]. The weight of evidence strongly supports that WSW are at risk from acquiring HPV from both their female partners and from current or prior male partners, and thus are at risk for cervical cancer. Both the Centers for Disease Control and Prevention and the American College of Obstetrician Gynecologists recommend routine Pap smear screening among WSW in the same manner as is performed for heterosexual women.

Based on recent convenience surveys of WSW, use of barrier protection between female partners appears to be very low despite the risk for STI transmission, particularly HSV and HPV, between female partners. In these surveys, 80% or more of women reported having never used barrier protection (gloves, dental dams) for digital sex or oral sex, and 60% or more of women never used barriers with sex toys or shared sex toy use [67–70]. Little is known about the knowledge, attitudes, and choices of protective and risk-reduction behaviors across different populations of WSW. Table 13.1 summarizes potential modes of transmission for the major bacterial, protozoal, and viral STI between female partners and risk-reduction strategies that WSW may use to reduce their risk of STI acquisition.

Pertinent Clinical Issues Unique to Population

Many studies report lower utilization of health services and cervical cancer screening among adult and adolescent WSW, especially those who

Table 13.1 Summary of potential modes of transmission for the major bacterial, protozoal, and viral STI between female partners and risk reduction strategies that WSW may use to reduce their risk of STI acquisition

Infection	Potential modes of transmission	Activities that may result in transmission between female partners	Risk reduction strategies
Chlamydia, gonorrhea	Shared cervicovaginal or anorectal fluids	Digital-vaginal sex Digital-anal sex Shared vaginal or anal sex toys	Use of barriers (gloves, condoms) on sex toys or during digital—genital contact Avoid sharing sex toys Clean toys between partners Use a new barrier on toys when changing activities or partners
Trichomonas	Shared cervicovaginal fluids	Digital-vaginal sex Shared vaginal sex toys	Use of barriers (gloves, condoms) on sex toys or during digital—genital contact Avoid sharing sex toys Clean toys between partners Use a new barrier on toys when changing activities or partners
Herpes simplex virus (HSV) type 1 and 2	Skin-to-mucosa contact Skin-to-skin contact	Oral–vulvo/vaginal sex Digital-vulvo/vaginal sex Digital-anal sex Genital–genital contact	Use of barriers (gloves, condoms) during digital—genital contact Use of barriers ("dental dams") during oral–genital contact
Human papillomavirus (HPV)	Skin-to-skin contact	Oral–vulvo/vaginal sex Digital-vulvo/vaginal sex Digital-anal sex Genital–genital contact? Shared vaginal or anal sex toys	Use of barriers (gloves, condoms) on sex toys or during digital—genital contact Avoid sharing sex toys Clean sex toys between partners Use a new barrier on toys when changing activities or partners Use of barriers ("dental dams") during oral–genital contact

identify as lesbian or have had exclusively female partners [7, 57, 60, 61, 71]. Sexual minority women (self-identified as lesbian or bisexual) participating in NHANES 2001–2010 reported being less likely to have a source of care, more likely to be uninsured, and to have worse self-reported health than heterosexual participants [72]. Data from the Behavioral Risk Factor Surveillance Survey 2000–2007 compared individuals in same-sex relationships to individuals in opposite-sex relationships. Women in same-sex relationships were significantly less likely to have health insurance coverage, were less likely to have had a checkup within the past year, were more likely to report unmet medical needs, and were less likely to have had a recent mammogram or Pap test [61].

Many reports have highlighted health disparities and the multiple barriers to care for sexual and gender minority persons. Barriers may include structural factors that impair access to health care (financial, lack of access to health insurance individually or with same sex partners); stigma, discrimination, and lack of nondiscrimination policies; reluctance to disclose sexual or gender identity; and a paucity of culturally competent providers and culturally appropriate prevention services [73–76]. In a recent survey of academic faculty practices accredited by the Liaison Committee on Medical Education, very few had existing policies (4%) or procedures (9%) to identify LGBT competent physicians in their institution. Only 16% reported having a comprehensive LGBT competency training and 52% reported having no LGBT training available at all [77]. Comprehensive research on the health of women with female sex partners across all dimensions of sexual identity

remains sparse. Based on a review from Coulter et al., from 1989 to 2011 the National Institutes of Health funded 628 studies concerning LGBT health. Once excluding projects about HIV/AIDS and sexual health, only 0.1% of all NIH-funded studies concerned LGBT health, and of the LGBT studies only 13.5% studied sexual minority women [78].

Assessing any woman for her risk of STI must incorporate an open discussion of all aspects of sexuality, including a lifetime history of sexual partners and practices, and not just those limited to preconceptions or stereotypes on the part of providers. Sexual and reproductive health services that are sensitive to gender minority women across a wide range of ages and populations are needed, including adolescents and college-aged women.

Bacterial vaginosis (BV) is a common, clinically pertinent condition among WSW, and there has been an expanding debate on whether BV can be transmitted between female sex partners and thus be considered an STI among WSW. The basic science and clinical aspects of BV among WSW will be reviewed in detail below.

Prior studies have suggested a higher prevalence of BV among WSW, although these studies had previously been limited to specific populations such as STD clinics or sexual health centers. Prevalence of BV among WSW in these studies ranged from 8 to 52% [32–34, 79–82]. In the largest sample to date, NHANES 2001–2004, a nationally representative sample of the U.S. civilian population, women who reported a lifetime history of a female sex partner had a prevalence of BV of 45.2% (35.5–57.5%) versus 28.8% (26.8–31.0%) in those not reporting a female sex partner [9].

Many studies have shown a high level of concordance of BV between a woman and her female sex partner (both partners with BV or both partners without BV) [79, 82–84]. A systematic review and meta-analysis examining the association between BV and female sexual partners found that having a history of female sex partner(s) conferred a twofold increased risk of BV (RR = 2.0, 1.7–2.3) [85]. Exchange of vaginal fluid among female partners or other shared behaviors may contribute to the initiation of BV. Among WSW, prior studies have found an association of BV with a higher lifetime number of female sexual partners, a history of receptive oral–anal sex, not always cleaning an insertive sex toy between uses, and smoking [82, 83, 86]. A recent observational study of community-based WSW aged 16–35 found those with BV were more likely to report a partner with BV (RR = 2.55, $p < 0.001$), sharing vaginal insertive sex toys (RR = 1.53, $p = 0.011$), >1 female sex partner in past 3 months (RR = 1.58, $p = 0.15$), and vaginal lubricant use (RR = 1.51, $p = 0.08$). No association was seen with age, race, smoking, hormone use, douching, vaginal intercourse, receptive oral or anal sex, and number of partners [87].

In a recent study that measured BV acquisition in a prospective cohort study of 199 WSW over one year, risks for incident BV were presentation ≤ 14 days since onset of menses, report of new sex partner with BV history, change in vaginal discharge, and detection of any of several BV-associated bacteria (BVAB) in vaginal fluid at enrollment [16]. Detection of *Lactobacillus crispatus* at enrollment conferred reduced risk for subsequent BV. Detailed analysis of behavioral data suggested a direct dose–response relationship with increasing number of episodes of receptive oral–vulvovaginal sex [16]. The Women on Women's (WOW) Health Study enrolled 289 WSW, including 122 women who were co-enrolled with their female sex partner, with vaginal swabs collected every 3 months over a period of 2 years. Prevalent BV was 27% at study entry with an incident case rate of 9.75 per 100 woman-years. Incident BV infection was associated with a new sex partner, having a partner with BV symptoms, receptive oral sex, and the onset of BV symptoms. Of particular note, women who were co-enrolled with a BV negative partner were much less likely to have incident BV (AHR 0.26, 95% CI 0.11–0.61) and had a high concordance of Nugent score category (normal flora, intermediate flora, BV) between co-enrolled partners, which was predominantly normal flora [88]. In a separate analysis of WOW Study participants who collected once weekly

vaginal swabs for three weeks, co-enrolled WSW were less likely to have BV, and concordance of Nugent score category was associated with a relationship of >6 months and sexual contact more than once per month [84].

Molecular methods have allowed a more detailed analysis of specific vaginal flora and flora shared between partners. Using both culture methods and strain typing with repetitive element sequence-based PCR (rep-PCR) fingerprinting, Marrazzo et al. [19] examined *Lactobacillus* colonization at vaginal and rectal sites and whether unique *Lactobacillus* strains are shared by female sex partners. Among 392 women, 25.3% had BV and most (58%) reported only one female partner during the prior six months. *L. crispatus* was the most commonly isolated lactobacilli, followed by *Lactobacillus gasseri* and *Lactobacillus jensenii*. Relative to *L. crispatus*, the rectum was more commonly the sole site of *L. gasseri* colonization. Detection of *L. gasseri* was associated with recent receptive digital-vaginal sex and increased BV risk (OR = 4.3, 1.4–13.4). Within this study, both members of monogamous partnerships were enrolled. Of 31 couples monogamous for ≥ 3 months, strains of genital lactobacilli by rep-PCR fingerprinting were identical in both members in 23 (74%). No similarities in lactobacilli strains were seen between "control" partners matched for age and date of enrollment to the study. Couples with identical *Lactobacillus* strains reported fewer female partners in the prior year. There was a trend towards an association of reporting use of shared vaginal sex toys and sharing identical lactobacillus strains. The likelihood of sharing identical lactobacilli was not related to mean age of the couple; number of lifetime male sex partners; or to practice, frequency, or timing of other types of sexual behaviors, including oral or anal sexual practices.

Several studies have examined the impact of specific sexual practices on the vaginal microflora among WSW and non-WSW. Among a cohort of community-based WSW, baseline vaginal colonization (by culture based method) with *Gardneralla vaginalis* was associated with >20 digital-vaginal sex acts in past 3 months or >10 toy–vaginal acts in past 3 months. There was no association of *G. vaginalis* colonization with oral–vaginal or anal–vaginal sex practices. Vaginal use of insertive sex toys and sharing of sex toys was associated with decreased quantities of H_2O_2 producing-*Lactobacilli* and a higher risk of colonization with *G. vaginalis* [89]. In an observational cohort of WSW, women treated for BV were reexamined 3–8 weeks post treatment. A full 40% still had BV (treatment failure) and only 27% were colonized with *L. crispatus* or *L. jensenii* post-treatment by PCR analysis. Reported interval sex practices were common (48% oral-vaginal 59% digital-vaginal; 18% penile-vaginal; 20% toy-vaginal), but there was no association between interim sex practices and the presence or absence of *L. crispatus* or *L. jensenii* at followup. Among women colonized with *Lactobaciili* at followup, report of receptive oral sex and digital-vaginal sex was associated with lower concentrations of vaginal *L. crispatus* [90].

An observational cohort of sexually experienced and sexually inexperienced women (including both WSW and non-WSW) examined associations between prevalent BV, BV-associated bacteria, and sexual behaviors. Six of eight candidate BV bacteria were absent or rare in vaginal samples from women with no reported history of sexual exposure (coital or non-coital) and showed increasing odds of detection with increasing levels of sexual activity and/or number of lifetime partners. Presence of *Megasphaera-1* in vaginal samples was independently associated with reporting a female sex partner in the past year and with having >10 lifetime sex partners [15].

Extra-vaginal reservoirs of vaginal bacteria may also be a risk factor for incident BV. In a case control study examining BV acquisition in a cohort of community-based WSW, detection of *G. vaginalis* in oral cavity or anal samples and *Leptotrichia/Sneathia* species in anal samples at enrollment was more common among women who subsequently developed BV during followup. *L. crispatus* was detected more frequently in anal samples among women who did not develop BV (controls) [18].

Despite an initial treatment response, BV commonly recurs or persists in both the short term [91–94] and long term [95, 96]. One study found that a past history of BV, a regular sex partner throughout the study, and female sex partners were significantly associated with recurrence of BV and abnormal vaginal flora [95]. A study of young WSW with BV treated with vaginal metronidazole gel examined behavioral and microbiologic correlates of persistent BV and abnormal vaginal flora at one month post-therapy. After adjustment for treatment adherence, detection of either BVAB3 or *Peptoniphilius lacrimalis* at baseline remained associated with the likelihood of BV persistence. Persistence was not related to any specific sexual activity, including male or female partners, use of sex toys, condom use, receptive oral or anal sex, or a sex partner with BV [17]. Among women (21% with a history of a female partner in past year) participating in a BV treatment trial, recurrence of BV was associated with having the same pre/post-treatment sexual partner, inconsistent condom use, and was reduced with use of estrogen-containing contraceptive [94].

Several prior clinic-based studies have examined the role of treatment of partners of females with BV in reducing persistent or recurrent BV. These trials enrolled women with male sex partners and involved treating women and their male partners with clindamycin [97], metronidazole [98, 99], or tinidazole [100] with followup ranging from 3 to 12 weeks. None of these trials have shown any benefit in reducing persistent or recurrent BV by treating male sex partners. The only proven interventions that have demonstrated an effect in preventing the development or recurrence of BV are chronic suppressive metronidazole therapy [96] and circumcision of male partners [101]. To date there have been no reported trials examining the potential benefits of treating female partners of women with BV, and thus no data on which to base a recommendation for partner therapy in WSW.

There has been one published trial utilizing a behavioral intervention to reduce persistent BV among WSW. Enrolled women were randomized to an intervention designed to reduce sharing of vaginal fluid on hands or sex toys following treatment for BV. Shared vaginal use of sex toys was infrequent among both groups. Despite the fact that women randomized to the intervention were 50% less likely to report receptive digital-vaginal contact without gloves than controls, there was no reduction in persistent BV at one month post-treatment or incident episodes of recurrent BV among women randomized to the intervention arm versus controls [102].

In summary, BV is common among women in general and even more so among women with female partners. Current data shows that women can share strain specific genital bacteria with their female partners and that specific bacterial species are associated with new infection and with treatment failure in BV. Recent data highlight the potential impact of sexual practices and sexual partnership characteristics on the vaginal microbial environment and that even extra-vaginal reservoirs of BV-associated bacteria may play a role in the development of BV or transfer of BV-associated flora between partners. Sexual behaviors that facilitate the transfer of vaginal fluid and/or bacteria between partners may be involved in the pathogenesis of BV, but more research needs to be done to understand the relationships between the transmission of BV-associated bacteria, BV pathogenesis, outcomes, and potential behavioral and medical interventions to reduce the occurrence, persistence, and recurrence of BV among WSW.

Screening and Diagnostic Recommendations

WSW are at risk of acquiring bacterial, viral, and protozoal STI from both female and male partners. Women who have sex with women should not be presumed to be at low or no risk for STI based on stated sexual orientation. Effective screening requires a comprehensive and open discussion of sexual and behavioral risks, beyond sexual identity, between care providers and their female clients.

Report of same sex behavior in women should not deter providers from considering and

performing screening for STI, including *C. trachomatis*, in their clients according to current guidelines. Sexual transmission of HSV-1 and HSV-2 can occur between female sex partners, and this information should be included in the counseling and evaluation of women's sexual health. Routine cervical cancer screening should be offered to all women, regardless or sexual orientation or partner choice, and women and girls should be offered HPV vaccine as per current guidelines. Although BV is common among WSW, routine screening for BV is not currently recommended. The evaluation of WSW who present with symptoms concerning for STI is no different than that for women with male only partners and may include testing for common vaginal infections (BV, vaginal candidiasis) and STI (chlamydia, gonorrhea, trichomoniasis) in this population.

An improved understanding of the dynamics of the healthcare interaction between WSW patients and providers would be extremely useful. Little is known about the knowledge, attitudes, and behaviors that contribute to STI screening and health care access among WSW, either from the perspective of women themselves or from the providers who serve them. Valuable research could provide information on women's perceptions of STI risk, reproductive health needs, and patterns of seeking preventive sexual health care. These data are essential to inform both women and their health care providers about STI risks and prevention and to foster a dialogue that could support sexual health in general.

Unique Treatment Considerations

STI and vaginal infections such as BV in WSW are treated in the same manner as in women with male sex partners. Diagnostic testing for and treatment of STIs and common vaginal infections remain the same for same sex and opposite-sex partnerships. Partner management for WSW with a known or suspected STI is part of comprehensive management, similar to that in opposite-sex partnerships. All partners should be offered testing and appropriate treatment guided by the source partner's diagnosis. Data continues to emerge regarding the potential for BV-associated bacteria to be shared between female partners and regarding the impact of common sexual practices among WSW on vaginal microbial flora which may impact acquisition or recurrence of BV. Encouraging awareness of signs and symptoms of BV in women and encouraging healthy sexual practices (barrier use, limiting or cleaning shared sex toys) may be helpful to women and their partners.

Conclusion

As emphasized above, the database on sexual health and STI among WSW, while growing, remains small when compared to other populations. More accurate information from future research on population health and STI among women could be obtained by routinely examining measures of sexual orientation including sexual behaviors, sexual attraction, and sexual identity, particularly as they relate to participation in sexual networks [75]. Larger population-based studies are needed to more clearly define the epidemiology and transmission risks for STI among the diverse group of women who have sex with women, including adolescents and young women. Specifically, further research is needed to identify risks that may predispose to the acquisition and transmission of *C. trachomatis* in this group and to better quantify the epidemiology of chlamydia infection among WSW in the United States. Women who have sex with women have a higher prevalence of BV, and more research needs to be done to understand the relationships between the transmission of BV-associated bacteria, the pathogenesis of BV, and treatment outcomes. In addition, future research is needed to identify behavioral and medical interventions which can reduce the occurrence, persistence, and recurrence of BV among WSW.

An improved understanding of the knowledge, attitudes, and behaviors that contribute to STI screening and health care access among WSW, either from the perspective of women

themselves or from the providers who serve them, would be highly desirable. Valuable research could provide information on women's perceptions of STI risk, reproductive health needs, and patterns of seeking preventive sexual health care. These data should help to inform WSW and their healthcare providers about STI risks and prevention, and to meaningfully contribute to a dialogue aimed at enhancing sexual health in this understudied population.

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Youth

14

Zoon Wangu and Katherine K. Hsu

Introduction

Youth are at high risk for acquisition and transmission of sexually transmitted infections (STIs) and HIV as well as unintended pregnancy. Youth in developed countries including Canada, the United Kingdom, France, Sweden, and the United States have generally similar rates of sexual activity; however, American youth have higher rates of pregnancy, childbearing, abortion, and STIs [1]. These rates are affected by various factors including negative societal attitudes toward teenage relationships and sexuality, restricted access to and high cost of reproductive health services, indecision regarding contraception, and lack of motivation to avoid pregnancy [1]. High rates of STIs among U.S. youth are associated with an increased number of sexual partners, lower levels of condom use, and complexity of their sexual networks [2].

HIV-infected youth represent a heterogeneous group in terms of sociodemographics, mode of HIV infection, sexual and substance abuse history, clinical and immunologic status, psychosocial development, and readiness to adhere to medications. Success in the treatment and prevention of pediatric HIV has completely changed the epidemic in high-resource countries, and perinatally-infected children can now survive into adulthood with appropriate care [3]. However, among U.S. youth aged 13–24 years living with HIV, the majority acquired their infection through high-risk behaviors, not through perinatal exposure [4].

Youth are in a unique period of development —their psychosocial developmental stage is normally associated with increased risk-taking behaviors and desire for autonomy [5], a key part of why they are so susceptible to STIs. Those who are HIV-positive can then enter into a "perfect storm" for additional STI acquisition, transmission, and related complications. STIs are known to enhance HIV shedding at mucosal sites, therefore increasing the infectiousness of the HIV-positive individual. In addition, STIs can have a more rapid and severe course in infected and immunosuppressed youth [6]. This review, therefore, focuses upon the epidemiology of sexual behaviors and STIs, biological and cognitive susceptibility to STI acquisition, STI screening and vaccination recommendations, and STI treatment and management considerations, in the key population of HIV-positive youth

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living in the U.S. Two case examples are also provided to illustrate intertwining STI/HIV risks and acquisition in high-risk youth.

Epidemiology of Sexual Behaviors and STIs in HIV+ Youth

As mentioned above, in the United States, two distinct cohorts of HIV-infected youth exist—those who acquired disease perinatally (PHIV-infected youth), and those who acquired the disease behaviorally (BHIV-infected youth), usually through sexual contact or injection drug use. Figure 14.1 presents the estimated distribution of youth and young adults aged 13–24 years living with diagnosed HIV infection at the end of 2014 by sex and transmission category, in the United States and six dependent areas [4].

Among male youth living with diagnosed HIV infection at the end of 2014 (N = 29,115), 80% of infections were attributed to male-to-male sexual contact. An estimated 12% had infection attributed to perinatal exposure. Three percent were attributed to heterosexual contact, 3% to male-to-male sexual contact and injection drug use, and 1% to injection drug use. One percent of males aged 13–24 had infection attributed to other transmission categories (including hemophilia, blood transfusion, or unreported/unidentified factors). Among adolescent and young adult females in the same time period (N = 9,241), 49% of infections were attributed to heterosexual contact. An estimated 42% of females aged 13–24 were living with diagnosed HIV infection attributed to perinatal exposure. Five percent were attributed to injection drug use, and 4% had infection attributed to other transmission categories as described above.

Risk and Protective Sexual Behaviors

Sexual risk behaviors have been examined separately in PHIV-infected and BHIV-infected youth. Carter et al. reviewed 32 articles published from 2001 to 2012 that described prevalence, correlates, and characteristics of sexual activity, HIV status disclosure, and contraceptive and condom use among U.S. infected youth aged

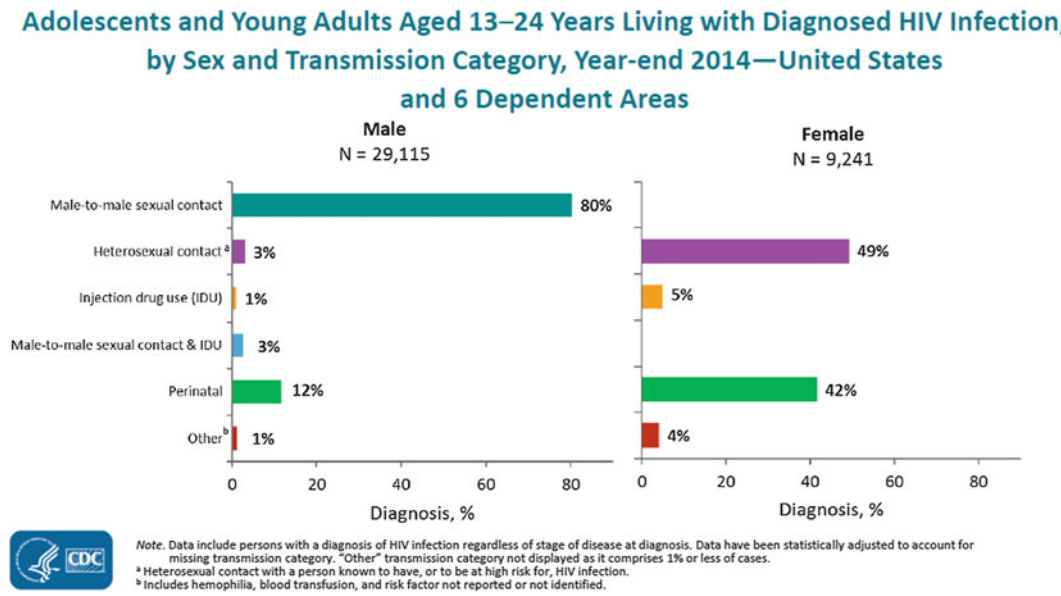

Fig. 14.1 Adolescents and young adults aged 13–24 years living with diagnosed HIV infection by sex and transmission category, year-end 2014—US and 6 dependent areas. From CDC, HIV surveillance in adolescents and young adults (through 2015). Available at: http://www.cdc.gov/hiv/pdf/library/slidesets/cdc-hiv-surveillance-adolescents-young-adults-2015.pdf

10–24 years [7]. By definition, most BHIV-infected youth (89% in one reviewed study) were sexually active in the previous year; 68–72% were sexually active in the preceding 3 months. A smaller proportion of PHIV-infected youth (both males and females) were sexually experienced (estimates ranged between 25 and 46%), and initiation of penetrative sex appeared to be slower compared to HIV-uninfected but PHIV-exposed youth, particularly for youth with HIV+ caregivers. However, one correlate of sexual initiation in PHIV-infected youth included antiretroviral non-adherence (among adults it has been suggested that this association may be related to hopelessness) [8]. Positive correlates of recent sexual activity in HIV-infected youth included acquiring HIV behaviorally (as compared to perinatally), drug and alcohol use, greater HIV knowledge, and physiological anxiety (as opposed to health-related anxiety). Those with mid-level CD4 counts (as opposed to very low or high CD4 counts) were less likely to be currently sexually active [7].

Partner concurrency has been identified as an issue in HIV-infected youth. Concurrency is a situation in which more than one sexual partnership is occurring simultaneously (in contrast to serial monogamy, in which each partnership must end before the next starts) [9]. A larger proportion of young BHIV-infected men who have sex with men (MSM) compared to BHIV-women who have sex with men (WSM) reported sex partner concurrency (56 vs. 36%); these numbers contrast sharply with the 14% concurrency rate reported in sexually active adolescents in the National Longitudinal Study of Adolescent Health [10]. Sexually active BHIV-infected female youth reported a mean of 1.8–1.9 partners in the previous 3 months; the same studies indicated that these young women thought their partners were also having other partners 22–36% of the time [7]. Concurrency is described in more detail below (see Biological and Cognitive Susceptibility to STI Acquisition).

Condom use and serostatus disclosure have been explored as protective factors. In general, condom use in PHIV-infected youth was more common compared to HIV-uninfected peers, but many PHIV-infected youth (65%) still reported ever having had condomless sex [7]. In studies of BHIV-infected youth, estimates of recent condomless sex ranged from 40 to 63%, with lower rates of condom use at last sex reported in WSM versus MSM (61 vs. 78%) [10]. Serostatus disclosure to recent sex partners estimates range from 20 to 60%, for both BHIV and PHIV-infected youth, and has been associated with fewer numbers of sex partners, the partner being primary/main versus casual, the partner being perceived to have HIV, greater number of sex acts with a partner, greater length of time since HIV diagnosis, disclosure to friends and family, immunosuppression, and older age [7].

STI Incidence and Prevalence

STI incidence and prevalence have been examined separately in PHIV-infected and BHIV-infected youth. In a cohort of 174 sexually active PHIV-infected adolescent girls aged 13–19 years, estimated cumulative incidences for STIs over a 6-year time period were calculated to be condyloma 8%, trichomoniasis 7%, genital chlamydia infection 6%, genital gonorrhea 4%, and syphilis 2%. Only 58% had a Pap test, but of those who did, 47.5% of the sexually active adolescents had abnormal cytology (30% occurred at first exam) [11]. Only one other pilot study in the U.S. has examined HPV in PHIV-infected children: of 23 PHIV-infected non-sexually active girls, 30 and 17% had anogenital and oral HPV (mostly high-risk types), respectively; of 23 PHIV-infected non-sexually active boys, 17 and 4% had anogenital and oral HPV, respectively (again, mostly high-risk types). Sexual activity was defined as oral, vaginal, anal or genital–genital contact in this study [12].

In BHIV-infected youth, one study of 143 BHIV-infected females aged 13–24 years screened over 18 months for genital chlamydia, gonorrhea, trichomoniasis, and syphilis calculated overall STI incidence to be 1.4/100 person-months, not significantly different between the high and low viral load groups. This was thought to be lower than previously

published estimates from high-risk non-HIV-infected youth. However, after initial diagnosis, 8/27 participants were diagnosed with 1 additional STI, indicative of ongoing sexual risk behaviors in a subset of the population [13].

The Reaching for Excellence in Adolescent Care and Health (REACH) study enrolled 346 BHIV-infected adolescents (257 girls and 89 boys) aged 12–18 years compared to 182 (142 girls and 40 boys) HIV-uninfected but same-aged, at-risk sexually active adolescents matched for drug-taking behaviors. Enrollment took place from 1996 to 2000 from 16 clinical sites around the U.S., and provided valuable longitudinal information about BHIV-infected adolescents as compared to high-risk peers. Incident trichomoniasis (1.3 vs. 0.6/100 person-months) and genital chlamydia infection (1.6 vs. 1.1/100 person-months) were significantly higher in BHIV-infected girls, though genital gonorrhea was not (0.6 vs. 0.4/100 person-months) [14]. Younger age was associated with STIs in both the BHIV-infected and HIV-uninfected girls. Incidence of genital gonorrhea was borderline significantly higher in BHIV-infected boys (0.8 vs. 0.2/100 person-months); genital chlamydia incidence was not (1.3 vs. 0.8/100 person-months), probably owing to the small number of male participants. No studies on STI incidence in BHIV-infected youth incorporated extragenital testing, so all of the above estimates are likely underestimates of true STI incidence that should also include oral or rectal infections.

In the REACH study, viral STI detection rates, specifically for HPV infection, were also significantly different in the BHIV-infected adolescents compared to the HIV-uninfected, at-risk sexually active adolescents. At baseline, 103 of 133 (77%) BHIV-infected girls, compared with 30 of 55 (55%) HIV-uninfected girls, were positive for HPV (predominantly high-risk types) from cervical lavage samples [15]. Prolonged persistence of either prevalent or incident HPV infection (measured every 6 months) was identified in BHIV girls (689 vs. 403 days, respectively); this persistence was associated with CD4 immunosuppression and the presence of multiple HPV types [16]. Patterns of HPV-type infection, clearance, and persistence did not differ in this cohort of girls before or after the introduction of HAART, but the median follow-up time after HAART initiation in the study was 428 days (since 70–90% of HPV infection in healthy women clears between 12 and 24 months, the authors speculated the study's 13-month follow-up time was too short to observe a significant difference in HPV clearance following HAART initiation) [17]. In terms of anal HPV, the BHIV-infected adolescents initially had a higher prevalence of anal HPV infection compared to the HIV-uninfected adolescents (girls: 59/183 (32%) versus 11/82 (13%) respectively; boys: 28/58 (48%) versus 9/25 (36%), respectively). HIV infection was independently associated with prevalent abnormal anal cytology results in the boys [18]. When followed annually over time, BHIV-infected girls had a significantly higher incidence of anal HPV versus high-risk HIV-uninfected girls (30 vs. 14 per 100 person-years), high-risk anal HPV (12 vs. 5.3 per 100 person-years), and anogenital warts (6.7 vs. 1.6 per 100 person-years); anal dysplasia was also more common but not statistically significantly different (12 vs. 5.7 per 100 person-years). Incident HPV and HPV-related events were consistently higher in the BHIV-infected boys versus high-risk uninfected boys [anal HPV (40 vs. 24 per 100 person-years), high-risk anal HPV (27 vs. 11 per 100 person-years), anogenital warts (8.8 vs. 1.2 per 100 person-years), and anal dysplasia (37 vs. 13 per 100 person-years)] but did not achieve statistical significance likely due to the small number of boys followed [19].

Seroprevalence of hepatitis B and C infection has also been examined in the REACH study [20]. BHIV-infected males were more likely to have evidence of HBV infection (defined as a positive HBV core antibody) than HIV-uninfected males (23.7 vs. 0%, respectively, $P = 0.008$). No significant difference was found for HBV infection in BHIV versus HIV-uninfected females (17.4 vs. 8.4%, respectively, $P = 0.112$). The rate of HCV infection (1.6%) (defined by positive EIA confirmed by repeat EIA, recombinant immunoblot, or PCR) was too small to make comparisons between

groups. A significant risk factor for HBV infections for males was a homosexual or bisexual orientation. For females, a risk factor for HBV infection was having more than 10 lifetime sexual partners. In addition, in the HIV-infected cohort, 15% of females and 36% of males who were seropositive for HBV had evidence of active HBV infection (defined as a positive HBV surface antigen); none of the HIV-uninfected subjects who were seropositive for HBV had evidence of active HBV infection.

Biological and Cognitive Susceptibility to STI Acquisition in HIV+ Youth

Youth are susceptible to acquisition of STIs based on several biological and cognitive/behavioral characteristics. In HIV-positive youth, STIs can promote increased HIV shedding and transmission to partners, making these characteristics particularly important.

Biological Factors

The female genital tract has a greater surface area than the male genital tract and a larger amount of semen compared to vaginal fluids is involved in intercourse [21, 22]. This accounts for some of the increased risk for female acquisition of HIV and other STIs. During puberty, the vaginal flora pH decreases and becomes more acidic secondary to the appearance of *Lactobacillus* species, though the relationship between this change and risk of STIs has not yet been clarified [23]. The cervix of female adolescents is lined by immature single-layered columnar epithelium, or cervical ectopy (also termed ectropion), which is more susceptible to infection compared to the multilayered squamous epithelium of adult women. Epidemiologic studies have found a specific association between ectopy and infection with *Chlamydia trachomatis*, as this organism resides in and favors columnar epithelial cells [24–26]. *Neisseria gonorrhoeae* may also attach preferentially to columnar epithelium rather than squamous tissue [27]. Persistence of ectopy has been associated with use of hormonal contraceptives (including both oral and injectable methods) which is of particular concern in female youth, many of whom utilize these medications [28].

The vasculature within columnar epithelium of ectopy is more superficial and more easily traumatized than that of squamous epithelium, theoretically permitting HIV-infected cells from the circulation to gain access to the mucosal surface, and for infected monocytes and lymphocytes to reach the circulation [23]. Ectopy has been associated with increased risk for HIV acquisition in uninfected women in some studies, particularly in the youngest age groups, although this remains controversial [29–31]. In one particular study of HIV-infected versus uninfected adolescent women, an independent association between HIV infection and increased ectopy was not shown [32].

Compared to older women, adolescent women have less estrogenization of the genitalia, thinner cervical mucus, and poor lubrication with intercourse-related trauma, all increasing their risk of STI acquisition. In addition, thinner mucus may permit organisms to penetrate more easily and to attach to mucosal sites or gain access to the upper reproductive tract of young women [23]. In a study of adolescent women and cytokine profiles in cervical secretions, lower concentrations of IL-10 were noted in HIV-uninfected versus HIV-infected subjects coinfected with HPV. The lower concentrations of IL-10 in the HIV-uninfected subjects reflected an appropriate response (shift from antibody-mediated genital immune environment to T cell-mediated immune response in the context of a viral infection). Concentrations of IL-12 (which enhances the cell-mediated response) were associated with HIV and HPV infections and presence of another STI (including *C. trachomatis*, *N. gonorrhoeae* and/or *T. vaginalis*). Thus, compared to their HIV-uninfected counterparts, in HIV-infected adolescent women there was a change in the local immune environment after secondary infection with viruses, bacteria, or protozoans [33].

Lastly, compared with adults, youth differ in their timing of acquisition and response to HIV

infection. For those with BHIV, youth are more likely than adults to be relatively recently infected [34]. Once infected, youth have persistence of thymic function; this allows for naïve T cell generation and a greater capacity for reconstitution especially in the context of highly active antiretroviral therapy (HAART) [35–38]. Of note, young women tend to have lower viral loads compared to young men despite comparable CD4 cell counts [39].

Cognitive/Behavioral Factors

Several aspects of adolescent development make youth more susceptible to STIs compared to their adult counterparts, and these are magnified in those infected with HIV. Those aged 14–17 years (middle adolescence) in particular may believe in the "myth of invulnerability," or that in the case of STIs, infections might occur to others but not to them. Youth also tend to be less knowledgeable regarding signs and symptoms of STIs and may be afraid to disclose their diagnosis and/or sexual activity to guardians or parents [28]. Peers and friends with whom youth associate may have a significant effect on their behavior and sexuality. For example, youth who believe that their friends are sexually active are more likely to become sexually active themselves, and having sexually active friends has been associated with earlier sexual debut among both boys and girls, controlling for a variety of social and demographic factors [40, 41].

Behavioral factors increasing the risk of acquisition of STIs in youth include having new, recent and/or multiple sexual partners; older age partners; partners who engage in high-risk behaviors (intravenous drug use); douching; drug use (including illicit and intravenous drugs, tobacco, and alcohol); and a past history of STIs [28]. Mood disorders and drug use are both common among youth. In those with a chronic illness such as HIV, depression is often secondary to long-term disease-related stressors and challenges, increasing the risk for substance use and abuse and thus STI acquisition [42, 43]. Furthermore, in a study of 166 HIV-infected youth aged 13–21 years in three US cities, a larger proportion of participants with BHIV compared to PHIV reported lifetime use of alcohol, marijuana, tobacco, and club drugs. Of note, this difference was not solely due to age [44]. This is consistent with national data demonstrating high rates of drug use among youth at risk for HIV in the first place [45].

As mentioned previously, concurrency is a key issue in HIV-positive youth. Since youth typically have more relationship partners than adults, sexual networks and concurrency are particularly important in this population and underlie the generally increased risk for STIs that youth face [46]. Concurrency amplifies the transmission of STIs and HIV by reducing the time between transmissions. By linking individuals together to create a large network, it removes any protection that would be afforded by monogamy, and pathogens can travel efficiently and rapidly throughout the population [47–50].

Age mixing of couples is an additional factor influencing the prevalence of curable and incurable STIs and one particularly relevant to youth. For example, age mixing is often asymmetric among heterosexual couples, with males being typically older than their female partners. Sex-based and economic power differentials may underlie the types of sexual relationships young women engage in, especially with older men, who may be more likely to be infected with HIV and other STIs in the first place [28, 51, 52]. In this way, such females will become infected earlier than their male age peers, as seen with HIV in many sub-Saharan African countries and in curable STIs in the US [9, 23]. Similar age mixing has also been shown to influence the spread of HIV among men who have sex with men [53, 54].

STI Screening and Vaccination Recommendations in HIV+ Youth

Close screening and follow-up is recommended for all of the STIs in HIV-positive youth because of their risk factors and because they are at

increased risk to transmit their HIV. Recommendations from the HIV Medicine Association of the Infectious Disease Society of America, the Centers for Disease Control and Prevention, the National Institutes of Health, Advisory Committee on Immunization Practices, American Association for the Study of Liver Diseases and the Infectious Disease Society of America are all applicable to this age group [55–60].

Gonorrhea, Chlamydia, and Syphilis Infections

All HIV-infected women aged <25 years should be screened for chlamydia and gonorrhea. HIV-infected youth should be screened for gonorrhea and chlamydia infection at initial presentation to care and then annually if at risk for infection; and for syphilis at care entry and periodically thereafter depending on risk factors [56, 57]. HIV-infected MSM are recommended to have even more frequent screening at 3–6 month intervals at all exposed anatomic sites (urethra, rectum, and oropharynx) if risk behaviors persist, if they or their sex partners have multiple partners, or if an STI is identified [57]. Secondary to high reinfection rates, rescreening in three months is indicated in men and women found to be positive for gonorrhea or chlamydia infections [57].

Optimal detection of genital tract infections caused by *C. trachomatis* and *N. gonorrhoeae* in men and women is achieved with the use of nucleic acid amplification tests (NAATs) which have superior sensitivity and adequate specificity compared to older nonculture and non-NAAT methods. These FDA-cleared and recommended tests can be collected via vaginal (provider-collected vs. patient-collected) or cervical swabs from women and first-catch urine from women or men [61]. However, first-catch urine from women may detect up to 10% fewer infections when compared with vaginal and cervical specimens [62–64]. Specimens obtained with a vaginal swab are the preferred type for female screening; they are as sensitive and specific as cervical swab specimens [63–68]. Urine is the preferred specimen type for male urethral screening [62]. While NAATs have not been cleared by the FDA for the detection of rectal and oropharyngeal infections, CDC recommends this testing based on increased sensitivity and ease of specimen transport and processing. Most reference laboratories have already performed internal validation for such testing which is now commercially available [62]. Table 14.1 shows the current FDA-approved platforms for NAAT testing of chlamydia and gonorrhea and the approved age ranges as relevant to youth.

Trichomoniasis

Unlike in HIV-uninfected patients, sexually active HIV-positive women should be screened for trichomoniasis at care entry and then at least annually thereafter. This is based on studies of women 18–61 years of age regarding the role of this organism in HIV transmission and the ability of trichomonas treatment to reduce genital HIV-1 shedding even in women not on antiretroviral therapy [69–72]. In addition, secondary to high reinfection rates, retesting in 3 months is indicated in women with trichomoniasis.

A few platforms offer sensitive and specific testing for trichomonas. NAAT has the highest sensitivity and acceptable specificity and is available for women only from vaginal, endocervical or urine specimens; however, the APTIMA assay may be used with male urine or urethral swabs if validated per CLIA regulations. Table 14.1 shows the current FDA-approved platforms for NAAT testing of trichomonas and the approved age ranges as relevant to youth.

Other FDA-cleared tests to detect *T. vaginalis* in vaginal secretions include the OSOM®Trichomonas Rapid Test (Sekisui Diagnostics, Framingham, MA) which relies on immunochromatographic antigen detection of *T. vaginalis* in vaginal secretions. This CLIA-waived point-of-care test provides results in 10 min, with a sensitivity of 82–95% and specificity of 97–100%. The Affirm™ VP III (Becton Dickinson, Sparks, MD) is a DNA hybridization probe test that evaluates for *T. vaginalis*, *Gardnerella vaginalis*, and *Candida*

Table 14.1 Food and drug-administration-cleared[a] specimen types and age specifications for the detection of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* by nucleic acid amplification test (NAAT) type[b]

FDA-cleared NAAT		FDA-cleared specimen types	FDA-cleared specimen types
Chlamydia/Gonorrhea NAATs	Abbott RealTime CT/NG (Abbott Molecular Inc., Des Plaines, IL)	Asymptomatic women: clinician-collected vaginal swab, patient-collected vaginal swab in a clinical setting, and urine Asymptomatic men: urine Symptomatic women: endocervical swab, clinician-collected vaginal swab, patient-collected vaginal swab in a clinical setting, and urine Symptomatic men: urethral swab and urine	No age range specified
	Aptima COMBO2® CT/GC assay (Hologic/Gen-Probe Inc., San Diego, CA)	Asymptomatic and symptomatic women: endocervical swab, clinician-collected vaginal swab, patient-collected vaginal swab in a clinical setting, gynecologic specimens collected in PreservCyt solution and urine Asymptomatic and symptomatic men: urethral swab and urine	Performance of vaginal swab and PreservCyt Solution liquid Pap specimens has not been evaluated in women less than 16 years of age
	BD ProbeTec™ ET CT/GC Amplified DNA assay (Becton Dickinson and Company, Sparks, MD)	Asymptomatic and symptomatic women: endocervical swab and urine Asymptomatic and symptomatic men: urethral swab and urine	No age range specified
	BD ProbeTec™ Qx CT/GC amplified DNA assay (Becton Dickinson and Company, Sparks, MD)	Asymptomatic and symptomatic women: endocervical swab, patient-collected vaginal swab in a clinical setting, gynecologic specimens collected in BDSurePath or PreservCyt solution and urine Asymptomatic and symptomatic men: urethral swab and urine	Performance of vaginal swab specimens has not been evaluated in patients less than 17 years of age
	Xpert® CT/NG assay (Cepheid, Sunnyvale, CA)	Asymptomatic and symptomatic women: endocervical swab, patient-collected vaginal	Performance has not been evaluated in patients less than 14 years of age

(continued)

Table 14.1 (continued)

FDA-cleared NAAT		FDA-cleared specimen types	FDA-cleared specimen types
		swab in a clinical setting, and urine Asymptomatic and symptomatic men: urine	
	Cobas® CT/NG test (Roche Diagnostics, Indianapolis, IN)	Asymptomatic and symptomatic women: endocervical swab, patient-collected vaginal swab in a clinical setting, clinician-collected vaginal swab, gynecologic specimens collected in PreservCyt solution and urine Asymptomatic and symptomatic men: urine	No age range specified
Trichomonas NAATs	Aptima® *T. vaginalis* assay (Hologic/Gen-Probe Inc., San Diego, CA)	Asymptomatic or symptomatic women: clinician-collected vaginal swab, clinician-collected endocervical swab, gynecologic specimens collected in PreservCyt solution and urine	Performance has not been evaluated in women less than 14 years of age
	BD ProbeTec® TV Qx Amplified DNA assay (Becton Dickinson, Franklin Lakes, New Jersey)	Asymptomatic or symptomatic women: clinician-collected endocervical swab, patient-collected vaginal swab in a clinical setting, and urine	Performance has not been evaluated in pregnant women or in patients less than 18 years of age

[a]FDA-cleared NAATs and specimen types as of March 2017
[b]Adapted from [61]

albicans in vaginal secretions. Trichomonas test sensitivity is 63% and specificity is 99.9%, and results are typically available in 45 min. However, methods for *T. vaginalis* diagnosis including the DNA hybridization probe test, wet mount, or culture have lower sensitivity and specificity and are not recommended as first-line screening tests if amplified molecular detection methods are available [57].

Human Papillomavirus (HPV)

High rates of Human Papillomavirus (HPV) persistence occur in all women with HIV infection and most women are first infected during adolescence. This has important implications for future development of invasive cancer. Thus, HIV-infected women should be screened for cervical cancer with a cervical Pap test within 1 year of sexual debut *regardless of mode of HIV acquisition*, but no later than age 21, since HIV positive sexually active women <21 years have a high rate of progression of abnormal cytology. The Pap test can be repeated at 6 months (and should occur twice in the first year after initial HIV diagnosis) but typically is repeated annually if baseline results are normal. HPV co-testing is currently not recommended for women younger than 30 years of age, but reflex HPV testing is

indicated if ASCUS (atypical squamous cells of uncertain significance) is found on Pap smear [58].

Lastly, all HIV-positive individuals should be vaccinated against HPV at ages 13 through 26 with bivalent, quadrivalent or nonavalent vaccine in a three-dose series, if these individuals did not receive an age-appropriate number of doses when they were younger [58–60].

Viral Hepatitis

HIV-infected patients should be screened for evidence of Hepatitis B infection upon entry to care (via detection of surface antigen, surface antibody and antibody to Hepatitis B core antigen). Those who are susceptible to infection should be vaccinated. Surface antibody testing should be performed 1–2 months following vaccine series completion, and a repeat series of vaccine should be considered for those who are nonimmune despite vaccination. Vaccination should also be reviewed and recommended for nonimmune sexual partners of those who are positive for Hepatitis B surface antigen. Lastly, patients who are positive only for anti-HepB core can be tested for chronic infection via HBV DNA and those without chronic infection should be vaccinated [56, 59, 60].

All HIV-positive patients should be screened for Hepatitis C infection via antibody testing; annual screening should be done for those who remain at risk. Those with positive antibody should be tested for HCV RNA to assess for active disease [56]. However, because a small percentage of HIV-infected patients do not develop antibody, RNA testing should also be considered for those with negative antibody and unexplained liver disease [57].

Hepatitis A vaccination is recommended for all susceptible men who have sex with men (including youth and adults) and others susceptible to disease (injection drug users, persons with chronic liver disease, travelers to countries with high endemicity or patients coinfected with other viral hepatitides). Hepatitis A total or IgG antibody testing should be done at 1–2 months after vaccination, and repeat series is recommended in seronegative individuals [56, 59, 60]. Limited data show that vaccination of those with advanced HIV or chronic liver disease may result in lower antibody concentrations and vaccine efficacy. In addition, in those with HIV, antibody response can be directly related to CD4+ levels [58].

STI Management and Treatment Considerations in HIV+ Youth

General Concerns About Treatment, Counseling, Confidentiality, and Sexual History-Taking

Important differences in STI treatment in HIV-infected youth exist as compared to their uninfected counterparts. For example, treatment for bacterial STIs is largely similar in both HIV-positive and negative patients, but follow-up testing is generally more frequent in HIV-infected patients. Viral and parasitic STIs may need a longer treatment duration in HIV-infected patients. Additional issues to consider during STI treatment for both HIV-infected youth and adults include condom use (e.g., clindamycin cream for treatment of bacterial vaginosis may weaken condoms, making them less useful for prevention of HIV/STI transmission and unintended pregnancy), alcohol use (e.g., importance of avoidance during treatment with nitroimidazoles), and risk of pregnancy while on STI therapy (e.g., implications of becoming pregnant while on potentially teratogenic HIV treatment regimens and transmission of STIs to the fetus).

In regards to *counseling* youth during STI management, clinicians must be nonjudgmental, use youth-oriented terminology and language, and be aware of motivational issues which worsen barriers to healthcare access. Youth already face multiple barriers to accessing quality STD prevention and management services including inability to pay, lack of transportation, long waiting times, conflicts between clinic hours and work/school schedules, and embarrassment attached to seeking STD services [73]. Concerns

about *confidentiality* are particularly important when caring for minors. Laws in all fifty states and the District of Columbia allow minors to consent to testing and treatment for sexually transmitted diseases without parent/guardian notification, but states may have differing laws regarding HIV testing or treatment. For example, California, New Mexico, and Ohio limit authorization to HIV testing but not treatment, and Iowa requires that parents be notified should their child test positive for HIV [74]. Clinicians must be familiar with state-specific laws in order to counsel and reassure minors about confidential services. Youth are likely to feel more confident and comfortable disclosing their sexual history and risk factors to a clinician if they can be assured of confidentiality as the law allows. It is important to recognize that while medical professionals including students report comfort with *sexual history-taking*, they report discomfort and lack of confidence in discussing sex and sexuality with youth [75, 76]. At the same time, adolescents frequently find it difficult to initiate sexual health discussions with adults, including clinicians, and prefer that clinicians bring up these sensitive topics [77–79]. An observational study of audio-recorded conversations between 253 adolescents and 49 pediatricians at 11 clinics in North Carolina found that while 65% of all visits contained some sexual health content, the average time devoted to this content was only 36 s, and only 4% of adolescents had prolonged conversations with their physicians [80]. Of note, adolescents never initiated sexuality talk and often were reluctant to engage beyond minimal responses to direct questions. These findings are concerning for missed opportunities to educate and counsel adolescent patients on healthy sexual behaviors and prevention of sexually transmitted diseases and unplanned pregnancy.

Syphilis Infection

Syphilis treatment recommendations for HIV-infected individuals do not differ from the stage-based recommendations given for non-HIV-infected individuals, as no treatment regimen has proven more efficacious than the standard regimens given for HIV uninfected patients. Moreover, no adolescent or young adult-specific data exist. Primary, secondary, and early latent syphilis are treated with benzathine penicillin G 2.4 million units IM in a single dose; late latent and tertiary syphilis are treated with benzathine penicillin G in weekly doses of 2.4 million units IM for 3 weeks; neurosyphilis (including ocular or otic syphilis) is treated with aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 h or continuous infusion, for 10–14 days. The efficacy of non-penicillin-based regimens in HIV-infected individuals is unknown [81].

Although the interpretation of treponemal and nontreponemal serologic tests for persons with HIV infection is the same as for the HIV-uninfected patient, unusual serologic responses (high serofast, fluctuating false-negative serologic tests, delayed appearance of seroreactivity) have been reported in HIV-positive individuals. Moreover, HIV-infected individuals are followed more closely following treatment: primary and secondary syphilis-HIV coinfected patients should be evaluated clinically and serologically for treatment failure at 3, 6, 9, 12, and 24 months (not just at 6 and 12 months); latent syphilis-HIV coinfected patients should be evaluated clinically and serologically for treatment failure at 6, 12, 18, and 24 months (not just at 6, 12, and 24 months). If at any time, clinical symptoms develop or a sustained (>2 weeks) fourfold or greater rise in nontreponemal titers occurs, CSF examination should be performed and treatment administered accordingly. If nontreponemal titers do not decline fourfold within 12–24 months of primary or secondary syphilis, or after 24 months after treatment for latent syphilis, CSF examination and treatment can be considered.

Gonorrhea and Chlamydia Infections

Gonorrhea and chlamydia treatment recommendations for HIV-infected individuals do not differ from those given for non-HIV-infected individuals. Uncomplicated anogenital and pharyngeal

gonococcal infections should be treated with single doses of ceftriaxone 250 mg intramuscularly and azithromycin 1 g orally. Dual therapy is recommended to improve treatment efficacy and potentially slow the emergence and spread of cephalosporin resistance. Importantly, doxycycline (rather than azithromycin) is no longer recommended as part of dual therapy based on substantially higher prevalence of gonococcal resistance to tetracycline than to azithromycin among isolates in the United States [57]. If ceftriaxone is not available, then cefixime 400 mg can be given orally in a single dose in addition to azithromycin; however, this regimen is not appropriate for pharyngeal infections as cefixime has limited treatment efficacy in this situation (92.3% cure (95% CI = 74.9–99.1%) compared to 97.5% cure (95% CI = 95.4–99.8%) in anogenital infections) [82, 83]. A test of cure is only needed for individuals with pharyngeal gonorrhea treated with an alternative regimen; either culture or NAAT should be performed 14 days after treatment and any positive testing should be followed by antimicrobial susceptibility testing. Limited data exist regarding alternative treatment regimens for those with cephalosporin or IgE-mediated penicillin allergy, but may include dual treatment with oral gemifloxacin and azithromycin or intramuscular gentamicin and azithromycin; spectinomycin may also be used for anogenital gonorrhea if available [57].

Treatment for chlamydia infection includes either azithromycin 1 g orally in a single dose or doxycycline 100 mg orally twice daily for 7 days. Alternative regimens include 7-day regimens of oral erythromycin base (500 mg four times daily), erythromycin ethylsuccinate (800 mg four times daily), levofloxacin (500 mg once daily) or ofloxacin (300 mg twice daily). Of note, although routine screening of chlamydia from oropharyngeal sites is not recommended, it can be sexually transmitted from oral to genital sites [84, 85]. Thus, chlamydia detected from the oropharynx should be treated with one of the above-recommended regimens. The efficacy of any of the *alternative* regimens, however, is unknown for this indication [57]. Lastly, more recent retrospective studies have raised some concern about the efficacy of azithromycin for rectal chlamydia infections [86, 87]. However, more studies are needed comparing azithromycin and doxycycline before definitive recommendations can be made in this regard [57].

Although pelvic inflammatory disease (PID) treatment regimens do not differ between HIV-infected and uninfected individuals (a single dose of a third generation cephalosporin should be combined with 14 days of doxycycline, to be used with or without 14 days of additional anaerobic coverage with metronidazole), decisions surrounding inpatient versus outpatient management are more complicated in youth. Even in the absence of general inpatient admission criteria for PID such as high fevers and toxicity, pregnancy or inability to tolerate oral medications, or tubo-ovarian abscess, some adolescents may still warrant inpatient admission. Though the PEACH (Pelvic Inflammatory Disease Evaluation and Clinical Health) Trial is often cited as evidence supporting the idea that females with mild to moderate PID can be treated as outpatients safely and effectively, the mean of those participants younger than 19 years was 17.8 years, reducing the generalizability of the study to all adolescent populations [88]. Specifically, as mentioned above, those adolescents younger than 17 years are particularly impacted by the "myth of invulnerability" and developmental stage may hinder medication compliance if parent/guardian guidance or other supports are absent. Determination of whether youth can comply with outpatient management should be based on developmental stage and availability of support systems, and youth should be closely followed by clinicians if outpatient therapy is prescribed, to ensure compliance.

Trichomonas

As mentioned previously, trichomonas plays a significant role in both the acquisition and transmission of HIV and thus HIV-positive women should be screened and treated if positive (see Screening) [56, 57, 70–73].

A randomized clinical trial of HIV-positive women 18 years and older (mean age 40.1 years, ±9.4 years) with trichomoniasis showed that a single dose of metronidazole (2 g orally) was less effective than 500 mg twice daily for 7 days [89]. Thus, in order to improve cure rates, we would also recommend that HIV-positive adolescent women should be treated with the one week course of therapy rather than the single-dose therapy [57]. Given the prevalence of underage drinking, avoidance of alcohol consumption while on metronidazole and for 24 h after completion of therapy should be explicitly addressed, even with adolescents.

Bacterial Vaginosis

Bacterial vaginosis recurs with higher frequency in women who have HIV infection [90]. In addition, BV increases the risk for HIV transmission to male sex partners [91]. However, current recommendations do not advocate for treatment of asymptomatic BV, and women with HIV who have BV should receive the same treatment regimen as those who do not have HIV infection (metronidazole 500 mg orally twice daily for 7 days, OR metronidazole gel (0.75%) 5 g intravaginally daily for 5 days, OR clindamycin cream (2%) 5 g intravaginally daily for 7 days) [57]. Again, given the prevalence of underage drinking, avoidance of alcohol consumption while on metronidazole and for 24 h after completion of therapy (72 h if an alternative regimen containing tinidazole is used) should be explicitly addressed, even with adolescents. A 2009 pilot study investigated whether treatment of asymptomatic BV would have any impact on HIV-1 shedding in the genital tract of 30 women (median age 42.5 years) already virally suppressed on HAART without coinfection with other STIs [92]. The women were randomly assigned in a non-blinded fashion to observation versus treatment with metronidazole. At one month of follow-up, while treatment with metronidazole decreased the rate of asymptomatic BV, there was no statistically significant difference in HIV-1 shedding. Further study is needed before treatment of asymptomatic BV can be recommended in HIV-positive women.

Herpes Simplex Virus

HIV-infected patients may have prolonged or severe episodes of genital, perianal, or oral HSV and HSV shedding is increased in these patients. While antiretroviral therapy reduces severity and frequency of symptomatic genital herpes, frequent subclinical shedding still occurs [93, 94]. Suppressive antiviral oral therapy can decrease the clinical manifestations of HSV in HIV-infected patients as shown in studies of individuals aged 21–63 years [95–97]. However, in studies of men and women including those as young as 18 years, suppressive therapy does not reduce the risk for either HIV or HSV-2 transmission to sexual partners [98, 99]. Regimens for first clinical episode of genital herpes do not differ between HIV-negative and HIV+ individuals (one of the following regimens for 7–10 days: acyclovir 400 mg orally three times daily, or acyclovir 200 mg orally five times daily, or valacyclovir 1 g orally twice daily, or famciclovir 250 mg orally three times a day); however, daily suppressive therapy and episodic treatment are generally higher dose and/or longer (5–10 days duration) in HIV-positive versus HIV-negative patients [57]. For severe HSV disease or complications that necessitate hospitalization (e.g., disseminated infection, pneumonitis, or hepatitis) or CNS complications (e.g., meningoencephalitis), the recommendation is for acyclovir 5–10 mg/kg IV every 8 h for 2–7 days or until clinical improvement is observed, followed by oral antiviral therapy to complete at least 10 days of total therapy.

Human Papillomavirus

Those with HIV are more likely to develop anogenital warts compared to those who are uninfected [100]. HIV-positive patients may also have larger or more numerous lesions, might not optimally respond to therapy, and tend to have

more posttreatment recurrences [93, 101–103]. In addition, malignancies such as squamous cell carcinomas resembling anogenital warts are more frequent in those with HIV and may require biopsy [104–106]. Currently no data support altered genital wart treatment for HIV-positive patients compared to their HIV-negative counterparts [57, 58].

Viral Hepatitis

The course of liver disease is more rapid in HIV/HCV-coinfected persons and the risk of cirrhosis is nearly twice that of persons with HCV infection alone. Such patients receiving HIV therapy are typically treated for HCV after their CD4+ cell counts increase in order to optimize immune response [57]. Specific recommendations for management and treatment of Hepatitis C are available from the American Association for the Study of Liver Diseases and the Infectious Disease Society of America [61].

Persons with acute hepatitis B receive supportive care. Those with chronic infection may be placed on treatment and can achieve sustained suppression of HBV replication and remission of liver disease [107]. HIV-infected patients should be screened and vaccinated as mentioned above (see Screening and Vaccination Recommendations). Additional recommendations for management of persons coinfected with HIV and HBV are available [100].

Patients with acute hepatitis A generally require only supportive care although those with acute liver failure or dehydration may require hospitalization. Vaccination in susceptible populations is described above (see Screening and Vaccination Recommendations).

Partner Management: General Guidelines

Maintaining the health of not only HIV-infected youth but also their partners is critical. For both BHIV- and PHIV-infected youth, anonymous HIV partner notification and contact tracing and HIV testing are available through and supported by the public health system in many states, and should be offered. However, systems may not be perfectly designed for dealing with youth-specific issues. For example, youth partner comprehension of the meaning of positive and negative HIV testing and window periods may vary by developmental stage as well as by level of health literacy, therefore disclosure and interpretation of test results may take longer. Because youth are in the process of asserting their independence, they often desire support from friends or family, while holding simultaneous fears of rejection or judgment. Clinicians should, therefore, take their cues from youth, and offer additional support in assisting HIV+ youth and their partners with disclosure to friends and family, if desired [108].

Expedited Partner Therapy

Expedited partner therapy (EPT) is the process by which a clinician provides medication or a prescription for a patient to distribute to his or her partner(s) for the treatment of STIs. EPT is legal in most states but varies by type of STI covered [57]. US trials and a meta-analysis of EPT have shown reductions in reinfection of index case-patients compared with patient referral differing according to the type of STI and the sex of the index case-patient; across trials, reductions in chlamydia and gonorrhea prevalence at follow-up were 20 and 50%, respectively [109–112]. These studies have included women as young as 14 years and men as young as 16 years of age. As a high-risk group for STI acquisition, youth could benefit greatly from this intervention; several national organizations, therefore, endorse EPT usage as a strategy to improve treatment and outcomes in youth [113–116]. However, the use of EPT in *STI-HIV-coinfected youth* has not specifically been investigated, as EPT usage would be limited by concerns about ongoing undiagnosed HIV infection in the partners of HIV-infected individuals who might or might not respond to advice to seek subsequent health care including STI/HIV testing.

HIV Pre-exposure Prophylaxis

Pre-exposure prophylaxis (PrEP) is the preventive use of ART medications (specifically tenofovir-emtricitabine, or TDF-FTC) in HIV-negative patients at high risk for HIV acquisition. TDF-FTC was approved by the FDA in 2012 for PrEP in adults [117, 118]. CDC interim guidance for use was released for MSM in 2011, heterosexual adults in 2012 and injection drug users in 2013 [119–121]. Although the CDC PrEP guidance targets PrEP use in adults, TDF-FTC may be used off-label in those under 18 years of age. PrEP has been shown to be effective in reducing new HIV infections by 44–75% in adult MSM, heterosexuals and injection drug users taking daily PrEP [122–125]. PrEP has also been found to be an acceptable and feasible intervention in MSM as young as 18 years of age [126, 127]. The likely efficacy of TDF-FTC PrEP and immediate concerns about HIV acquisition in partners of HIV-infected youth should be balanced against data indicating that TDF-FTC adherence is lower in youth, and unknowns remain about impact on long-term bone mineral density or kidney function [128, 129]. Ongoing studies of PrEP in those under 18 years of age may lead to an indication for PrEP in younger youth in the near future.

While PrEP may be an effective HIV prevention method for both uninfected youth and discordant couples, barriers may exist to PrEP access. First, minors' access to PrEP without parent/guardian consent is unclear, as demonstrated by a review of laws current as of December 2011 [130]. No state specifically prohibits minors' access to PrEP or other HIV prevention methods and all states expressly allow some minors to consent to medical care for diagnosis or treatment of STIs. However, only eight jurisdictions allow consent to preventive or prophylactic services. Thirty-four states either allow minors to consent to HIV services or allow consent to STI or communicable disease services and classify HIV as an STI or communicable disease. Seventeen jurisdictions allow minors to consent to STI services, but they do not have a specific HIV provision and they do not classify HIV as an STI or communicable disease. Second, cost may also be a barrier for youth. While health insurance companies may cover PrEP, out-of-pocket costs may be up to $13,000 per year. Medicaid may cover PrEP depending on the state and medication may be covered via participation in clinical trials. Gilead, the manufacturer of tenofovir-emtricitabine, provides a co-pay assistance program which may help those eligible to cover the cost of co-pays.

Contraception and Family Planning Issues in HIV-Positive Youth

Family planning and reproductive healthcare are important issues for youth as they have a high rate of unintended pregnancies in general. As mentioned above, with the advent of effective antiretroviral therapy, PHIV-infected youth are surviving to adolescence and young adulthood. Thus, family planning becomes especially pertinent for both PHIV-infected and BHIV-infected youth particularly for prevention of perinatal disease.

Available studies show that reproductive health discussions with HIV-infected youth usually focus on STI prevention instead of family planning, and any pregnancy discussions tend not to occur in adolescents or in older women [131–133]. Clinicians may feel uncomfortable discussing sex and sexuality, and such barriers may prevent effective discussions surrounding family planning in HIV+ youth.

Importantly, drug interactions may occur between hormonal contraceptives and antiretroviral therapies, potentially increasing the risk of pregnancy in youth. Protease inhibitors can decrease the estrogen levels of combined hormonal oral contraceptives, and NNRTIs can either increase or decrease estrogen levels although the clinical significance of such effects are unknown [134, 135]. Failure of either drug or medication toxicities can occur in either situation. No such interactions occur between antiretroviral agents and depot medroxyprogesterone acetate (DMPA) or the levonorgestrel implant system [126]. Although case reports of

failure of etonogestrel implants with efavirenz has been reported, neither the WHO or CDC recommend restrictions on any form of birth control in HIV-infected women [136–138].

Case Illustrations

Case 1

A 17-year-old African-American female presented to the Pediatric Infectious Diseases clinic for persistent posterior cervical and postauricular lymphadenopathy. She had been seen by her pediatrician five months prior for right-sided axillary lymphadenitis which was drained and grew methicillin-resistant *Staphylococcus aureus*; she had MRSA lymphadenitis on the left side four months prior to the current visit. Her current adenopathy was nontender with no overlying skin changes; she had no complaints of pain and was otherwise asymptomatic. She had a history of genital herpes and chlamydia twice in the last two years, both of which were treated appropriately. She reported condomless sexual intercourse with a male partner within the last three months and had negative STI screening for chlamydia, gonorrhea, HIV, and syphilis five months prior. Her periods were regular. Physical exam at the time of evaluation was remarkable for nontender cervical, pre/postauricular and inguinal adenopathy. Lab testing showed a normal CBC, ESR, CRP, and a negative PPD; as she had reported interaction with her grandmother's new kitten, *Bartonella* and *Toxoplasma* titers were sent and negative as were EBV and CMV titers. RPR was nonreactive. HIV fourth-generation antibody/antigen testing was reactive; HIV viral load was 141K and CD4 count was 333 cells/mm^3 (16%).

The patient and her mother were called back to clinic for disclosure of her diagnosis and the pediatrician requested support by the infectious diseases team during the disclosure process. Significant tension between the mother and patient was noted during the visit with some apathy from the patient toward her diagnosis, and overwhelming anger in the mother. The care team discussed HIV, evaluation, testing and follow-up and set up another visit for the patient to return the following week for a second visit and follow-up testing. Partner notification and contact tracing was discussed with the patient but she refused, stating "I don't want to get him in trouble." It was noted that during her follow-up visit which she chose to attend without her mother, the patient appeared to be calm and coping relatively well with her diagnosis and agreed to start antiretroviral therapy. Her viral load became undetectable two months after diagnosis with an increase in her CD4 count to 448 cells/mm^3. However, during subsequent STI screening she tested positive twice for chlamydia and reported wanting to become pregnant "so that my boyfriend will never leave me." She stated he was unwilling to come to clinic with her but he did accept EPT for chlamydia.

Case 1 demonstrates a few challenges inherent in the care of the adolescent patient with behaviorally acquired HIV. First, this young woman is in a high-risk group for HIV acquisition as a young African-American female, and likely acquired HIV from her condomless heterosexual encounter (the most common transmission category for women). Confidentiality and seeing the adolescent alone seemed to improve the tone of the visit and likely contributed to her adherence and consistent follow-up visits. In this way, her evolving autonomy was respected and she contributed to decision-making in her own care. However, the fact that she became reinfected with chlamydia twice while remaining adherent to her HIV regimen demonstrates a lack of understanding and insight regarding those high-risk behaviors associated with HIV acquisition in the first place, and certainly increased the risk of transmission to her partner. While she did not share many details about her relationship, and it is unclear whether or not she was in a position to negotiate condom use with her boyfriend, her self-efficacy may have been remarkably reduced in the setting of an unhealthy relationship. Lastly, her concern regarding pregnancy in order to remain with her boyfriend demonstrates some elements of the "myth of invulnerability" and the feeling of "wanting to belong" common to the

adolescent age group. Regarding partner management, the patient expressed that the partner would accept EPT for Chlamydia. However, she did not want to involve her partner regarding HIV notification and contact tracing for fear of ramifications. As mentioned previously, anonymous partner notification and contact tracing are available through and supported by the public health system in many states. This was offered to the patient but unfortunately she did not accept even after emphasis on confidentiality, because she felt the partner "would know that I told on him." It is not clear whether the relationship was of an abusive nature, as the patient refused to share further details about her boyfriend or about the relationship in general.

Case 2

An 18-year-old Latino male presented to the Pediatric Emergency Room with fever, malaise, and sore throat. During evaluation he disclosed to the ER resident that he had engaged in anal intercourse with an anonymous male partner in the past two weeks. The patient was screened for syphilis, chlamydia, and gonorrhea including pharyngeal and rectal NAATs and HIV testing was sent. He was called back to the Pediatric Infectious Diseases clinic when rectal chlamydia testing and HIV testing were both positive. The patient was hesitant to come into the clinic visit and expressed that he knew testing was positive, but that he did not want to receive any treatment, and was ashamed of his sexuality. The patient did eventually come to clinic and was treated for rectal chlamydia and received counseling regarding his HIV diagnosis. After seeing the patient alone and reinforcing the fact that he had no viral resistance and was an excellent candidate for antiretroviral therapy, the patient agreed to start treatment and had an undetectable viral load within the next few months. He also requested that clinic staff be present and assist him with HIV diagnosis disclosure to his family, including his openly gay brother, although he was not yet comfortable disclosing his own sexuality. Four months after diagnosis he came to clinic with a complaint of a rash; he was noted to have erythematous lesions on his palms, soles, and scrotum. He had no neurologic findings on evaluation and was otherwise well. He also disclosed feeling very depressed about his diagnosis and that he had started to have anonymous sexual partners, all male, and had started using methamphetamine. The patient refused drug counseling or psychiatric support but remained in close touch with the pediatric social worker, with whom he developed a strong rapport. He was treated empirically for secondary syphilis at that visit. RPR titers were 1:64 and eventually declined to 1:2 one year after treatment, with no recurrence of symptoms or concern for reinfection. During clinic follow-ups he reported ceasing drug use and receiving support from his family regarding his sexuality, as he had finally decided to disclose to them and felt comfortable doing so on his own. Almost two years after diagnosis he still had an undetectable viral load, and had had negative STI screening since his syphilis diagnosis. He was referred to an adult infectious diseases practitioner for transition of care but continued to be seen in pediatric clinic for several visits until he became comfortable with the new care team. Since full transition 2.5 years after diagnosis, he continued to be seen regularly in follow-up and still had an undetectable viral load.

Case 2 shows another patient in one of the highest risk groups for both HIV and syphilis: a young Latino/Hispanic man who has sex with men (MSM). His mode of acquisition was also the most common for men acquiring HIV in the US. The patient had significant difficulty accepting his sexuality and wanted to be "normal," showing the adolescent's very common desire to "belong." This patient had comorbidities common to youth that could have potentially impeded his care—drug use and depressive symptoms. It was not until treatment for his depression and response to treatment was demonstrated, and his move from a large city to a small town, that we were able to optimize his HIV care and compliance to the point where his viral load became undetectable. Similar to Case 1, it also demonstrates the patient's lack of understanding and insight regarding those high-risk behaviors

associated with HIV acquisition, as the patient developed secondary syphilis after his HIV diagnosis and also had evidence of mild developmental delay. In addition, even if adolescents have some understanding of potential risks, the perceived benefits of new sexual relationships typically outweigh them. However, in this case the patient was compliant with his treatment and follow-up and was able to transition successfully to adult care with significant support from his pediatric care team. As described previously, another important issue in this case is that of disclosure to others, and the clinician team offered support to the patient while he told his family about his diagnosis.

Conclusions

Youth constitute one of the highest risk groups for STI and HIV acquisition and transmission as well as unintended pregnancy and are in a unique period of psychosocial development. This creates a "perfect storm" particularly in HIV-positive youth for additional STI acquisition and transmission. Effective interventions for decreasing high-risk activity must include acknowledgement of normal adolescent development as inclusive of sexual exploration, skillful identification of motivational issues, and a clear and mature addressing of the pertinent issues, all using youth-oriented terminology and language relevant to the specific youth patient's developmental stage [6]. Case-finding and screening for STIs among these youth are key, as coinfection with STIs remains common. Regardless of disease duration or mode of HIV transmission, every effort must be made to engage and retain HIV-infected youth and their partners in care and prevention, to improve and maintain long-term health, through and into their adult years.

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