AIDS Study Group/Spanish AIDS Plan consensus document on sexually transmitted infections in HIV-infected patients

Authors: Expert panel of the Grupo de Estudio de Sida (GESIDA: AIDS Study Group) and the Plan Nacional sobre el Sida (PNS: National AIDS Plan)*****.

Correspondence
Rosario Palacios Muñoz
UGC Enfermedades Infecciosas
Hosp. Virgen de la Victoria
Campus Teatinus, s/n
29010 Málaga
Tel: 951032594
Fax: 951032593
E-mail: rosariopalaci@gmail.com

Conflicts of interest: No private funding was obtained for the preparation of this manuscript.

Acknowledgments: Drs. Mª Jesús Barberá, Josefina López de Muniain, Martí Vall Mayans, Jorge del Romero and **Federación Estatal de Lesbianas, Gays, Transexuales y Bisexuales (FELGTB: National Lesbian, Gay, Transexual, and Bisexual Federation).**

***Members of the GESIDA and PNS Expert Panel**
All the members of the panel are authors of this article

Coordinators
Rosario Palacios, Hosp. Virgen de la Victoria, Málaga, Spain
Rosa Polo, Secretaría del PNS, Ministerio de Sanidad y Política Social, Madrid, Spain

Authors
Jose Luis Blanco, Hosp. Clinic, Barcelona, Spain
José Ramón Blanco, Hosp. San Pedro-CIBIR, Logroño, Spain
Xavier Camino, Hosp. Donosita, San Sebastián, Spain
Miguel Cervero, Hosp. Severo Ochoa, Leganés, Spain
Fernando de la Portilla, Hosp. Virgen del Rocío, Sevilla, Spain
Javier Ena, Hosp. Marina Baixa, Villajoyosa, Spain
Clotilde Fernández, Hosp. Puerta del Mar, Cádiz, Spain
Pedro Herranz, Hosp. La Paz, Madrid, Spain
Sara Villar, Hosp. Vall d'Hebron, Barcelona, Spain

Reviewers
Francisco Bru, Instituto de Salud Pública, Ayuntamiento de Madrid, Madrid, Spain
Pere Domingo, Hosp. de la Santa Cruz y San Pablo, Barcelona, Spain
Nuria Margall, Hosp. de la Santa Cruz y San Pablo, Barcelona, Spain
Guillem Sirera, Hosp. German Trias, Barcelona, Spain
Raúl Soriano, Secretaría del PNS, Ministerio de Sanidad y Política Social, Madrid, Spain
Pompeyo Viciana, Hosp. Virgen del Rocío, Sevilla, Spain

Summary

Sexually transmitted infections (STIs) are a major public health problem.

Given the high morbidity and potential sequelae associated with STIs in the short and long terms, physicians must have sufficient knowledge about management to ensure suitable prevention, diagnosis, and treatment. HIV infection is associated with STIs, not only in terms of the route of transmission, but also because STIs increase the risk of HIV transmission. In the present article, a panel of HIV specialists, dermatologists, proctologic surgeons, and microbiologists, on behalf of the Spanish AIDS Study Group (GESIDA) and the National AIDS Plan (PNS), summarizes the updated clinical practice guidelines for the evaluation, management, and prevention of STIs in HIV-infected patients.

Keywords: HIV, sexually transmitted infections, guidelines, recommendations, syphilis, human papilloma virus

Introduction

Sexually transmitted infections (STIs) are a major public health problem. The high morbidity and mortality associated with STIs and the possibility of sequelae mean that we must have sufficient knowledge to manage these diseases correctly, both in terms of prevention and in terms of diagnosis and treatment. Infection by the human immunodeficiency virus (HIV) is clearly interrelated with STI: both share a route of transmission and the increased risk of transmission of HIV can serve as an indicator of changes in sexual risk practices (1-3).

The present document aims to provide the scientific community and health professionals with updated knowledge to be able to manage those STIs that require greater attention because of their relevance in HIV-infection.

The document was prepared by an expert committee designated by the board of directors of the AIDS Study Group (GESIDA) and the Secretariat of the National AIDS Plan. The committee reviewed the most relevant data from scientific publications and conference presentations.

The strength and quality of the recommendations were classified following the recommendations of the Infectious Diseases Society of America and the United States Public Health Service (Table 1).

General Aspects

STIs comprise a group of infections caused by more than 25 microorganisms that are transmitted mainly via sexual relations. HIV infection is not merely another STI; the special interaction between HIV and other STIs (3-7) means that any evaluation of STIs in the HIV-infected patient requires special attention. Prevention of STIs requires both interventions designed to increase awareness of safe sexual behavior, as well as early diagnosis and treatment. As many STIs are silent, asymptomatic, or barely asymptomatic (at least at onset), early diagnosis involves initial and subsequent screening in asymptomatic HIV-infected patients. Table 2 sets out a list of screening tests for HIV-infected patients.

Recommendations for screening of STI in the HIV-infected patient

1. Screening for STI in the HIV-infected patient must include a detailed clinical history and complete physical examination. These must be particularly detailed in patients whose risk behavior implies a greater probability of having an STI (A-II).
2. The patient must be tested for syphilis, HAV, HBV, and HCV. Patients whose serology is negative for HAV and HBV must be vaccinated against both viruses (A-II).
3. Clinical samples from patients who, in their physician's opinion, engage in risk practices should be sent to the microbiology laboratory for STI screening (A-II).
4. HIV-infected women should be referred to a gynecologist (A-III).
5. STI screening should be performed annually in patients who engage in risk practices and every 3-6 months in high-risk patients (B-III).
6. HCV and syphilis serological testing should be performed yearly in patients with negative serology results (B-III).

Diagnosis and treatment of the main syndromes

Urethritis and cervicitis

Urethritis is a syndrome characterized by a mucopurulent urethral secretion, dysuria, or both, although it may be asymptomatic. It is classified as gonococcal urethritis (GU) and nongonococcal urethritis (NGU), although it may also have a noninfectious etiology. Cervicitis is the equivalent condition in women and is characterized by inflammation of the endocervical mucosa and discharge (8). The main causes of urethritis and cervicitis and the corresponding diagnostic methods are set out in Table 3 (8-11). The different therapeutic options for GU and NGU caused by *Chlamydia* are shown in Table 4.

Systematic follow-up of patients who have been correctly treated for infection by gonococcus and *Chlamydia* (with resolution of symptoms) and who have not had further contact with untreated individuals is only recommended in pregnant women

and in patients who have undergone treatment with erythromycin or amoxicillin. Patients should be followed up 3 weeks after finishing treatment (B-III) (10,11).

Recommendations for the management of urethritis and cervicitis in the HIV-infected patient

1. All symptomatic patients should be treated, even when microscopy does not confirm a diagnosis of infection (C-III).
2. All sexual partners during the previous 3 months should be screened and offered treatment (C-III).
3. Women who have had contact with a man infected by GU or NGU caused by *Chlamydia* should be treated empirically (B-II).
4. Patients should be interviewed 3 weeks after treatment to verify adherence and resolution of symptoms (B-III).

Orchitis and epididymitis

Orchitis is a viral or bacterial inflammatory process affecting the testicle. It may be unilateral or bilateral, is commonly associated with infection or inflammation of the epididymis, and is caused by entities such as gonococcus or *Chlamydia*.

Diagnosis is usually based on clinical symptoms, although evaluation can be completed using a blood and urine workup and Doppler ultrasound scan of the testicle (12). Urine culture is also frequently indicated, as is urethral sampling for gonococcus and *Chlamydia trachomatis*.

Treatment is based on hygiene measures and administration of anti-inflammatory drugs and analgesics, as well as antibiotics if the infection is bacterial. Although medical treatment is sufficient in most cases (8), surgical drainage should be applied in cases of abscess of the scrotum or testicles (12). In the case of infection by gonococcus or *Chlamydia*, sexual partners should also receive treatment (12).

Vulvovaginitis

Vulvovaginitis is an inflammation that affects the vulva, vagina, and ectopic endocervical tissue to differing degrees. It may or may not be infectious in origin. When it is, the most common manifestations are *Trichomonas* infection, candidiasis, bacterial vaginosis, and vaginosis caused by other microorganisms (herpes, gonococcus, *Chlamydia*) (8). Although vulvovaginitis by *Candida* and bacterial vaginosis are not classed as STI, their high incidence in HIV-infected women means that they are included in this group.

Table 5 compares the most frequent types of vulvovaginitis with the normal vagina and Figure 1 provides a diagnostic algorithm for abnormal vaginal secretion. Table 6 sets out the treatment of choice and therapeutic alternatives, in pregnancy and recurrences.

Follow-up is not necessary initially or after treatment in asymptomatic patients with trichomoniasis; the same is true of bacterial vaginosis if symptoms resolve. In candidiasis, follow-up is only necessary if symptoms persist or the patient experiences recurrences 2 months after finishing treatment.

Treatment of the partner and abstention from sexual relations is recommended until treatment of trichomoniasis has finished and the partner is asymptomatic. In vulvovaginitis caused by *Candida*, treatment must be considered if the patient has recurrent infections. Treatment is not recommended in bacterial vaginosis.

Inflammatory pelvic disease

Inflammatory pelvic disease is an infection of the upper genital tract and is generally considered a consequence of an ascending STI of the cervix, a polymicrobial infection associated with vaginosis, or an opportunistic infection by commensal perineal/vaginal flora in the context of a primary STI (13).

Diagnosis is mainly based on clinical symptoms and confirmed microbiologically using Gram stain and culture of a cervical smear in Thayer-Martin or similar

medium and screening for *C. trachomatis* with detection of antigen or genetic material or specific culture (13). Imaging techniques reveal the presence of masses, collections, hydrosalpinx/pyosalpinx, or fluid in the pouch of Douglas, and laparoscopy makes it possible to drain collections, obtain samples, visually examine the pelvis and adnexal structures, and make a differential diagnosis with other conditions.

When inflammatory pelvic disease is suspected, empirical antimicrobial therapy should be started early (A-Ib) (13) to cover gonococcus, *Chlamydia*, and anaerobes (B-III) (13). The regimen of choice is intramuscular ceftriaxone 250 mg combined with oral doxycycline at 100 mg/12 h for 14 days, with the option of adding oral metronidazole at 500 mg/12 h (A-Ib). An alternative regimen consists of oral levofloxacin 500 mg/24 h combined with oral metronidazole at 500 mg/12 h for 14 days (A-Ib). A tubo-ovarian mass should be drained by laparoscopy, surgery, or culdocentesis if it is located at the bottom of the pouch of Douglas in the following circumstances: size greater than 8 cm, no improvement after 72 hours of parenteral antibiotic therapy, or increase in size.

Genital ulcer

An ulcer is any lesion that leads to a loss of the integrity and continuity of the skin and/or mucosa. The etiology of genital ulcers is very varied and ranges from infection to toxicoderma or tumors (14). However, most cases in sexually active young people are caused by STIs, mainly genital herpes, primary syphilis, or chancroid (15). Table 7 shows the STIs that lead to genital ulcer disease (GUD), and their differential characteristics.

Therapy protocols for this condition in HIV-infected patients are similar to those used in the general population, although a higher number of therapeutic failures advise monitoring of these cases until they are completely cured (8). Figure 2 shows an empirical treatment algorithm for GUD.

Recommendations for the management of GUD in the HIV-infected patient

1. Sexually active patients with GUD should be tested for HIV infection (III-A).
2. When genital ulcer is suspected, an etiologic diagnosis should be made using microbiological examinations adapted to the individual epidemiologic situation and geographic location (III-A).
3. If it is not possible to apply standard microbiological techniques, simple diagnostic algorithms and treatment should be used. The individual patient's response to therapy should be monitored where possible (III-A).
4. In the patient with atypical genital ulcers or ulcers that do not respond to treatment after 2 weeks, a biopsy specimen should be taken for a histopathology study and any appropriate additional tests should be performed (III-A).
5. Patients should abstain from sexual relations until the genital ulcer is completely cured. This recommendation includes cases treated with single-dose regimens (III-A).

Infection by *Treponema pallidum*

Introduction

Syphilis is a systemic infectious disease produced by the spirochete *Treponema pallidum.* It is a public health problem throughout the world. The population group most affected by this disease is that of men who have sex with men (MSM) (16,17), and co-occurrence with HIV could have enormous clinical and epidemiological repercussions (18).

Classification

Syphilis is classified as congenital or acquired. Congenital syphilis is transmitted from mother to child in utero and is classified as early congenital syphilis (first 2 years of life) and late congenital syphilis, which includes the lesions of congenital syphilis. Acquired syphilis, whether by sexual contact or by transfusion, is classified as early syphilis (primary, secondary, and early latent), which is acquired during the previous 1-2 years (19,20), and late syphilis (late latent and tertiary), which develops over more than 1-2 years (19,20).

Symptoms

Primary syphilis is characterized by the development of an ulcer or chancre at the site of infection or inoculation after an incubation period of 10-90 days. Although generally a single painless lesion in the anogenital region, presentation may be atypical in HIV-infected patients, with multiple painful and destructive lesions outside the genital area (lips and mouth). Secondary syphilis develops 3-6 weeks after the appearance of a chancre at the inoculation site and manifests as nonpruriginous cutaneous exanthema affecting the palms and soles, together with flat condyloma, mucocutaneous lesions, and generalized lymphadenopathy. It can also develop with patchy baldness, uveitis, otitis, meningitis, cranial pair palsy, hepatitis, splenomegaly, periostitis, and glomerulonephritis. Latent syphilis does not present clinical manifestations. Late syphilis includes gummatous syphilis, neurosyphilis, and cardiovascular syphilis.

Diagnosis

Early syphilis is diagnosed based on the presence of *T. pallidum* in lesions or lymph nodes using dark field microscopy, direct fluorescence with monoclonal antibodies, or polymerase chain reaction (PCR) (21), which is the method of choice in late syphilis, especially in late tertiary syphilis and congenital syphilis.

Serology testing

Two serologic methods can be applied to test for nontreponemal antigens (cardiolipin antigen or reaginic testing): the rapid plasma reagin test (RPR) and the Venereal Disease Research Laboratory test (VDRL). Treponemal antigens are detected using the *T. pallidum* hemagglutination assay (TPHA), the *T. pallidum* particle agglutination test (TPPA), the fluorescent treponemal absorption test (FTA-Abs), and the treponemal enzyme immunoassay (EIA). Most of these methods are based on recombinant antigens that detect both IgG and IgM. There are also tests that detect anti-*T. pallidum* IgM antibodies.

EIA is recommended as a single diagnostic screening method (22). If there is a strong suspicion of primary syphilis, an anti-treponemal IgM test should be requested and repeated 1 or 2 weeks later if the result is negative. RPR/VDRL can be applied to screen patients with a low risk of infection; however, it is not useful for screening in high-risk patients, since the result may be negative due to the prozone phenomenon. When the disease is suspected, the prozone effect can be detected by diluting the sample. If used, RPR/VDRL should be carried out with undiluted serum and diluted serum to avoid false negatives, together with a recommended screening method. A positive result should be confirmed using a treponemal test based on an antigen other than that used in the screening test. When the confirmation test is positive, RPR/VDRL should be performed with quantification. If the result of RPR/VDRL is negative and there is a high suspicion of infection, a specific IgM EIA–type antitreponemal method should be applied. A positive IgM EIA result indicates active infection; if negative, the test does not rule out active infection, especially in late syphilis.

Recommendations for lumbar puncture in the HIV-infected patient with positive syphilis serology (B-II)

Lumbar puncture should be performed in order to examine the cerebrospinal fluid (CSF) of patients with positive syphilis serology results who also present one of the following:

- neurological symptoms possibly caused by neurosyphilis
- eye disorders possibly caused by ocular syphilis
- otologic symptoms possibly caused by syphilis
- CD4 lymphocyte count <350 cells/mm^3 and or serum RPR titer >1:32 (22-24)
- treatment failure

Criteria for the diagnosis of neurosyphilis

In HIV-infected patients, neurosyphilis occurs more frequently, progresses more rapidly, and develops with more atypical forms (25). In an appropriate clinical context, the presence of >5 mononuclear cells/mm^3 in CSF is suggestive of neurosyphilis. Unfortunately, 40-60% of HIV-infected patients can present pleocytosis or increased CSF protein in the absence of syphilis (25). A count of >20 mononuclear cells/mm^3 is more commonly associated with spirochete

infection than with HIV infection. VDRL in CSF is considered the gold standard test for the diagnosis of syphilis; its sensitivity can be as low as 30% (23).

Treatment

HIV-infected patients should receive the same regimen as HIV-negative patients (8, 23, 26). Penicillin is the treatment of choice, although the regimen varies with the stage of syphilis (8, 26).

Syphilis in pregnant women

All pregnant women should undergo testing to screen for syphilis at their first visit (26). Treatment should match the stage. Penicillin is the treatment of choice, even in patients who are allergic to it. Allergic patients should undergo desensitization before treatment (8,26). Treatment should be followed by serology testing in the third trimester and after delivery.

Treatment of sexual partners

All sexual contacts (oral, vaginal, or anal) in a person infected with syphilis, irrespective of the stage, should undergo a clinical and serological assessment (8,23,27). In primary syphilis, the contacts of the previous 3 months should be investigated; in secondary syphilis, the contacts of the previous 6 months should be investigated; and in the case of early latent syphilis, the contacts of the previous 12 months should be investigated.

In the case of patients with late latent syphilis, contacts from more than 1 year before should be investigated. Serology testing should be performed at the visit; if negative it should be repeated at 6 weeks and 3 months (27). The recommended period of sexual abstinence in these patients has not been defined (23).

Follow-up

Data on whether HIV infection affects the therapeutic and serological response of patients with syphilis are contradictory. Although some studies suggest that the

serological response to treatment is less favorable in HIV-infected patients (28, 29), its clinical significance is unknown, since it could be due to poorer clearance in nontreponemal tests than to poorer clinical efficacy (28). The criteria for cure have not been clearly established. We must remember that, although nontreponemal tests are usually negative, results can remain positive at low titers for a long period and even for life (serofast reaction) (28).

Primary, secondary, and early latent syphilis

Effective treatment is followed by a minimum 4-fold reduction in the titer of nontreponemal tests during the first 12 months after starting treatment. CSF should be tested to rule out neurosyphilis if the titer does not decrease 4-fold at 12 months, if it increases during the course of the disease, or if signs and/or symptoms persist or reappear (27). In all the above cases, treatment must be re-administered with 3 weekly doses of penicillin G, unless the CSF study indicates neurosyphilis (8).

Late latent syphilis

If the titer has not fallen 4-fold at 12-24 months, CSF should be analyzed.

Neurosyphilis

Patients with neurosyphilis who present pleocytosis before starting treatment should undergo CSF testing every 6 months until values return to normal (8). The return to normal CSF lymphocyte values seems to be the earliest marker of response to treatment (26). Normalization of VDRL titers is slower, especially in patients with CD4 <200 cells/mm^3 and in those who are not receiving antiretroviral therapy (ART) (18). HIV-infected patients are 2.5 times less likely to return to normal values for VDRL in CSF than non–HIV-infected patients (18). It is unknown whether the lack of a return to normal VDRL levels in CSF is indicative of therapeutic failure (18).

Syphilis during pregnancy

Pregnant women should undergo serology testing during weeks 28-32 and at delivery (8). Women with a high risk of reinfection should undergo monthly testing (8).

Therapeutic failure

Therapeutic failure is defined as recurrence or persistence of clinical manifestations, absence of a ≥4-fold fall in the titer of nontreponemal tests at 24 months after treatment of latent syphilis, or a ≥4-fold increase in the titer of these tests at any time during treatment (26). In patients with neurosyphilis, treatment must be re-administered if the CSF leukocyte count has not returned to normal 6 months after completing treatment or if VDRL titers in CSF remain reactive 2 years after treatment (26).

Syphilis, HIV infection, and ART

Although the serological response is slower in HIV-infected patients, it does improve in patients taking ART, for whom the risk of developing neurosyphilis falls by 65% (30).

Table 8 shows the recommendations for treatment and follow-up of syphilis in HIV-infected patients. Figure 3 shows the diagnostic and therapeutic management and follow-up in pregnant women.

Recommendations on treatment of syphilis in the HIV-infected patient

1. HIV-infected patients should be treated with the same regimen as HIV-negative patients. Penicillin is the treatment of choice (A-II).
2. Penicillin is the treatment of choice in pregnant women, even in those who are allergic to it. In such cases, the patient should undergo desensitization before treatment (A-III).
3. In patients with neurological symptoms, patients whose therapy fails, or both, lumbar puncture should be performed to rule out the possibility of neurosyphilis (A-III).

Infection by human papillomavirus

Introduction

Human papillomavirus (HPV) belongs to the genus *Papillomavirus* within the family Papillomaviridae. There are more than 100 HPV genotypes, of which 40 can infect humans via sexual transmission (skin, mucosa, vertical transmission, birth canal, fomites). These viruses are classified according to whether they are located on skin or mucosa and according to their oncogenic capacity (low, medium, and high risk).

Genital infection by HPV is the most common STI, and it is estimated that 80% of the population will become infected at least once in their lifetime (31), with the virus being acquired during the months immediately following the first sexual relation.

HPV infection can be symptomatic or asymptomatic and has been associated with different benign and malignant conditions such as warts/condylomas, recurrent respiratory papillomatosis (mother-to-child transmission), and squamous cell carcinoma. Cervical cancer is the most important public health problem that can lead to HPV infection. Although the number of cases of cervical cancer has fallen as a result of cytology screening, incidence remains high (32).

Epidemiology

The oncogenic role of HPV in anal cancer and cervical cancer is undeniable (33-36). HIV-infected patients are 2- to 6-fold more frequently infected by HPV, irrespective of their sexual practices and 7-fold more frequently have persistent infection, since their immunodepressed status prevents them from eliminating the virus (37).

In HIV-infected patients, the incidence of cervical intraepithelial neoplasia (CIN) has been reported to be greater than in non-HIV-infected patients (38). As a result of observations that associated cervical cancer with HPV infection in HIV-infected

patients, in 1993 the Centers for Disease Control and Prevention (CDC) defined the presence of CIN 2-3 as category B and the presence of invasive cervical cancer as category C (39). Squamous cell carcinoma accounted for 85-90% of all cases of cervical cancer, and HPV DNA was found in almost 100% of cases, the most prevalent genotypes being 16, 18, and 31 (33-36,40).

Anal cancer accounts for less than 5% of all cases of cancer of the digestive tract among the general population and is the fourth most common cancer in HIV-infected patients (32,41). Traditionally, the population groups most at risk of developing anal cancer were women and elderly persons; however, as soon as this disease was associated with HPV and sexual risk practices, studies performed among men who have sex with men (MSM) revealed an annual incidence of 35 cases per 100,000 men. This figure is similar to that of cervical cancer before smear tests began to be used (42). As is the case for cervical cancer, HIV-infected men and women have a greater prevalence of anal infection by HPV and of anal cyto/histologic lesions, a greater incidence of anal infection, with greater persistence of infection and more rapid progression of cyto/histologic lesions to cancer (33,41,43-45). Genotype 16 is the most frequent in these lesions, and simultaneous infections caused by several types are found in 73% of HIV-infected MSM and in 23% of HIV-negative MSM. Nevertheless, anal cancer has not been classed as an AIDS-defining disease.

HPV was first associated with squamous cell carcinoma of the oropharynx in 1983 (46) and, since then, several studies (47-49) have confirmed the etiologic/oncologic role of some types of HPV in a subgroup of head and neck tumors. HPV-associated squamous cell oropharyngeal carcinoma affects younger patients and is less related to classic risk factors. Similarly, the associated risk factors are number of partners since the start of sexual relations, oral sex, presence of anal diseases caused by HPV in the same patient, and having a stable sexual partner with CIN (49,50,51). Although infection of the buccal cavity by HPV in HIV-infected patients is relatively frequent (47,51-54), there have been no reports of an increase in cases of cancer of the head and neck in this population; however, the greater life expectancy resulting from ART could change the incidence and prevalence of this disease.

Lastly, in recent decades, HPV has been confirmed as the etiologic agent in at least 40% of cases of squamous cell carcinoma of the penis (55). The prevalence of HPV in this condition ranges from 30% to 80%, and it is greater in the HIV-infected population than in the general population (53,55,56). HPV-associated squamous cell carcinoma of the penis has been related to different risk factors, such as not being circumcised, number of sexual partners, having a sexual partner with cervical dysplasia, and HIV infection (56-61).

Pathogenesis

HPV is a DNA virus that infects the skin or mucosal epithelium. The viral genome encodes the capsid proteins (L1 and L2) and 6 proteins known as early proteins (E1, E2, E4-E7), which enable viral replication and the formation of viral particles (62).

Low-risk (LR) HPV—HPV 6 and 11—cause more than 90% of cases of condyloma and recurrent respiratory papillomatosis. Infection by low-risk HPV causes 100% of cases of uterine neck cancer, 50% of cases of cancer of the vulva, vagina, and penis, and 12% of cases of oropharyngeal cancer (Tables 9 and 10).

The HPV life cycle takes place in keratinocytes. Papillomaviruses have 2 types of replication. The first occurs in the basal cells of the epidermis, where DNA is maintained as a plasmid. Infection is termed nonpermissive, because the full cycle of viral replication has not taken place. The viral genome replicates once per cell cycle in synchrony with the chromosome of the host cell. This type of replication maintains a latent and persistent infection in the stem cells of the epidermis. The second type of replication, vegetative replication, occurs in the most differentiated cells of the epidermis, the keratinocytes, where large amounts of viral DNA are produced and later packaged to form new viral particles. In most cases, infection occurs without a malignant transformation. In such cases, viral DNA is maintained separate form the host DNA in the form of an episome. In the subgroup of HPV infections that progress to malignancy, viral DNA enters the host genome during progression to cancer. Carcinogenesis is associated with expression of proteins

E6 and E7, which inactivate tumor suppressor protein p53 and retinoblastoma protein, respectively (62).

Cytohistologic classification

Progression of HPV infection to cervical cancer is accompanied by a sequence of histologic changes. The nomenclature of the classification of cervical HPV-associated cytologic and histologic abnormalities has changed frequently. The currently accepted criteria—the Bethesda system (63)—are shown in Table 11.

As is the case with CIN, anal intraepithelial neoplasia (AIN) is classified as AIN 1 (involves the lower third of the epidermis), AIN 2 (involves the lower two-thirds of the epidermis), and AIN 3 (affects the whole epidermis). Similarly, following the Bethesda criteria (63), anal cancer can be classified according to the findings of anal cytology (Table 12).

Approximately 90% of carcinomas of the penis are squamous cell carcinomas, of which there are 3 subtypes: verrucous, condylomatous, and basaloid. As in the cervix and anus, invasive squamous cell carcinoma of the penis has precursor lesions, known as penile intraepithelial neoplasia (PIN), which can also be classified as PIN 1 (mild dysplasia), PIN 2 (moderate dysplasia), and PIN 3 (severe neoplasia and carcinoma in situ). PIN 3 in turn has 3 variants: bowenoid papulosis, Bowen disease, and Queyrat erythroplasia.

Diagnostic tests in HPV infection and related conditions

Table 13 summarizes the diagnostic tests used in HPV infection and related conditions (8,9).

Diseases associated with HPV infection

Cervix

Vulvovaginal condylomata acuminata

Vulvovaginal condyloma is associated mainly with LR-HPV 6 and/or 11 (64); its prevalence is higher in HIV-infected patients, who often have more than one type of HPV infection (65).

Treatment of vulvovaginal condyloma is indicated for symptomatic relief and/or psychological reasons. When the appearance of the condyloma points to underlying intraepithelial neoplasia or cancer, as well as lesions refractory to medical treatment, a biopsy should be performed before treatment is administered (66). In HIV-infected women, identification of vulvar condyloma highlights the need for a biopsy, due to the greater prevalence of high-grade neoplasm (67).

Two types of medical treatment are available:
- Cytodestructive therapy (destroys the tissue of the condyloma): topical treatment with liquid nitrogen (cryotherapy) or trichloroacetic acid.
- Immune-mediated therapy (helps the immune system to clear the condyloma): topical imiquimod, topical or injected interferon, and topical sinechatechins.

Surgery (excision or ablation) is reserved for:
- Absence of response to medical treatment.
- Extensive or bulky disease.
- Multisite disease affecting the vagina, vulva, or anus.
- Disease associated with intraepithelial neoplasm.

In HIV-infected women (37), the treatment of choice is topical imiquimod 5% cream.

In pregnancy, trichloroacetic acid is preferred, due to the absence of systemic absorption and fetal side effects. Recurrence is reduced when treatment is administered during the second half of pregnancy.

Cervical cancer

Screening for cervical cancer in HIV-infected women

HIV-infected women must undergo periodic gynecological monitoring, which should include an external examination, cytology sample, and biopsy of any suspected lesion of the vulva, vagina, and cervix (68).

The use of PCR in HPV infection determines how often cytology should be performed; therefore, if HR-HPV is detected, cytology should be performed every 6 months.

Initial colposcopy of the vagina, vulva, and cervix is recommended, due to the high risk of multifocal disease in HIV-infected women (69). The need for further colposcopy is based on the results of cytology.

Figure 4 shows the cervical cancer screening algorithm for HIV-infected women.

The combined use of cytology and PCR for HPV infection in risk populations such as HIV-infected women increases the efficacy of screening of cervical disease caused by HPV. Molecular techniques are recommended and should be performed in the following situations:

- HIV-infected patients with a normal cytology result who have a clinical history that indicates they are at risk of HPV infection.
- Cytology compatible with atypical squamous cells of undetermined significance (ASCUS).
- Post-conization monitoring.

Treatment

Treatment of CIN is based on the correlation between the results of cytology, colposcopy, and biopsy, as well as patient characteristics such as age, pregnancy, and the likelihood of adherence to treatment (70). If the colposcopy findings are not satisfactory, ablation cannot be applied, as a histologic examination of the

nonvisualized tissue is necessary to rule out occult neoplasm. In such cases, excision is recommended. Excision of recurrent disease is also recommended after ablation (71).

Figure 5 shows the therapeutic algorithm and follow-up of CIN (72).

Pregnancy and cervical lesions caused by HPV

Evaluation and treatment of precancerous lesions caused by HPV infection in pregnant women is different to that performed in women who are not pregnant, due to the risk that injury to the cervix could induce labor:

1. When cytology is compatible with ASCUS, colposcopy should be carried out during pregnancy or delayed until at least 6 weeks after delivery.
2. In the case of high-grade lesions (ASC-H) and low-grade squamous intraepithelial lesions (LSIL), colposcopy should be performed.

Therapy after colposcopy is as follows:

1. CIN 1: defer evaluation and treatment until 6 weeks after delivery.
2. CIN 2, 3: perform colposcopy and cytology every 3 or 4 months during pregnancy or defer until at least 6 weeks after delivery. Excision of abnormal tissue is not recommended during pregnancy.

Invasive cervical cancer

Treatment is as indicated for non-HIV-infected women and consists of surgery with (out) radiotherapy (73).

ART and cervical cancer

The highest-quality information on the effect of ART on CIN comes from the multicenter observational prospective WHIS study (74), which analyzed incident CIN regression to reveal a rate of 12.5% per year for patients on ART. The figure was greater in patients with a higher CD4 count and low-grade lesions. These findings show that CIN lesions are currently an indication for starting ART (75).

Recommendations for the management of cervical lesions associated with HPV infection

1. Imiquimod is the treatment of choice for genital condyloma, followed by surgery in cases where medical treatment fails. Extensive or bulky lesions should be excised (C-II). Biopsy should always be performed to rule out intraepithelial neoplasm at any site.
2. During the first year after diagnosis of HIV infection, 2 cervical cytology tests should be performed (one every 6 months); if the results of both are normal, annual cytology should be performed and should be accompanied by examination of the anus, vulva, and vagina (C-II).
3. Initial colposcopy should be performed (C-II).
4. If diagnostic testing is performed using PCR for HPV, detection of a high-risk oncogenic subtype means that cytology and HPV determination should be performed every 6 months (C-II).
5. Electrosurgical excision and ablation are the treatments of choice in patients with persistent CIN 1 or CIN 2-3 (C-II). Excision is the treatment of choice in cases where colposcopy is unsatisfactory and in recurrence after ablation (C-II).
6. After surgical excision, cervical cytology is indicated, as is colposcopy, with biopsy every 3 months (C-II).
7. Treatment of invasive cancer follows the same recommendations as in non-HIV-infected women (C-II).

Diseases of the anus

Condylomas or anal warts

Treatment of condylomatosis aims to destroy and remove the largest number of lesions with the least morbidity. Nonsurgical options include podophyllin and imiquimod (76). Giant condyloma acuminata (Buschke-Löwenstein tumor) is a separate entity that is most commonly associated with in situ carcinoma or even with invasive carcinoma (76). Patients should be referred to a coloproctologist for extirpation of the lesions. Skin plasty is often necessary.

Anal cancer

In an attempt to achieve the same results as for cervical cancer screening, a number of studies have been carried out in recent years to demonstrate similar usefulness for anal cytology to detect lesions suggestive of anal cancer. Despite current evidence, the indication for a screening technique remains controversial (41,43,77,78). For example, guidelines published by other scientific societies, such as the British HIV Association, do not recommend its generalized practice (79).

Recommendations on screening for anal cancer in HIV-infected patients (B-II)

1. Annual screening is recommended in
- HIV-infected MSM
- HIV-infected women with a previous diagnosis of cervical cancer or CIN 3.

2. Screening is desirable every 2-3 years in other risk groups who could potentially benefit from it, namely
- HIV-infected women
- HIV-infected men, irrespective of their sexual history
- Non-HIV-infected MSM
- Non-HIV-infected women with vulvar or cervical cancer
- Patients who are immunodepressed for other reasons, eg, transplant recipients

Given the poor availability of cytology, high-resolution anoscopy (HRA), and specially trained surgeons in most centers, diagnostic and treatment algorithms can only be established in experienced centers. In other centers, a digital rectal examination is the most acceptable and cost-effective approach in high-risk patients (44).

Figures 6 and 7 show the algorithm to be followed based on the findings of anal cytology, HRA, and anal biopsy (80). It is not clear whether it is useful to determine the presence of HPV DNA at the time of the cytology, since the only studies published were performed in small cohorts and provided contradictory results (both in favor and against) (81).

Treatment of high-grade lesions

Table 14 summarizes the therapeutic options available for the treatment of high-grade anal lesions (76,80,82).

ART and anal cancer

Few studies have analyzed the impact of ART on AIN, although the results of some of these lead us to believe that this therapy has little or no effect on outcome. Patients who take ART survive longer, with the result that anal epithelia are exposed for longer to the risk of cancer (HR-HPV, anal dysplasia, and cancer) (77,83).

Recommendations on screening and treatment of anal cancer in HIV-infected patients

1. The anus should be inspected and a digital rectal examination should be performed at least once per year in symptomatic HIV-infected patients, women undergoing screening for cervical cancer, and HIV-infected MSM (C-III).
2. Anal cancer screening based on anal cytology and inspection in the following cases (B-II):
- Annually in HIV-positive MSM
- Where possible, every 2-3 years in HIV-infected women, HIV-positive men irrespective of their sexual history, non-HIV-infected MSM, HIV-negative women with vulvar or cervical cancer and patients who are immunodepressed for other reasons not necessarily related to HIV, eg, transplant recipients.
3. Any patients with anal cytology revealing dysplasia (LSIL and HSIL) should undergo HRA, with multiple anal biopsies (C-II).
4. Periodic follow-up with HRA and cytohistologic specimens after ablation (B-II).

Other neoplasms associated with HPV infection

Oropharynx

Of all the tumors affecting the head and neck, the most commonly associated with HPV infection is squamous cell carcinoma of the tonsil followed by squamous cell carcinoma of the base of the tongue (46).

In its initial phases, oropharyngeal carcinoma is usually asymptomatic. When symptoms appear, the disease is usually in a very advanced stage. Oropharyngeal cytology has not proven useful as a screening method; therefore, no tool is currently available for the early diagnosis of this disease.
Given the scarce scientific evidence at this level, no recommendations can be made for the early diagnosis of oropharyngeal carcinoma.

Penis

Squamous cell carcinoma is the most common cancer of the penis, and a very high percentage of cases are associated with HPV, specifically types 16 and 18 (55,84).

Diagnosis is by biopsy when macroscopic lesions are evident. Very few studies have proposed using cytology of the penis for early detection of incipient lesions (54,85). The penis can be examined to locate subclinical lesions using staining with acetic acid 3% or 5%, followed by a visual examination to investigate whitish or erythematous lesions. In any case, neither cytology nor staining with acetic acid is currently established as a diagnostic or follow-up test.

Given the scarce scientific evidence, no evidence-based recommendations can be made. However, well-defined risk groups such as HIV-positive MSM, patients with a history of anal dysplasia/neoplasia, and men who are partners of women with cervical dysplasia/neoplasia should undergo a physical examination after staining with acetic acid 3% or 5%. Scientific evidence is insufficient to recommend cytology.

Vaccine against HPV

Prophylactic vaccines

Two vaccines are currently available for the prevention of HPV infection. Both have virus-like particles which induce a neutralizing antibody response that is 60 times greater than the natural infection: **Gardasil®** is a quadrivalent vaccine containing HPV 6, 11, 16, and 18 antigens, and **Cervarix®** is a bivalent vaccine containing HPV 16 and 18 antigens.

Several clinical trials have proven the efficacy of both these vaccines against HPV infection and against the development of precancerous lesions (86-91).
In terms of clinical efficacy, the impact of vaccines on the incidence of cervical invasive cancer and death has not been assessed. Even if prevention of both is the ultimate aim of vaccines, it will take several years until we know whether they can prevent the development of cancer.

The FDA approved the quadrivalent vaccine in June 2006, and the indication for its use was extended in September 2008 (92, 93).

The vaccine is indicated for females aged 9 to 26 years to prevent the following conditions: cervical cancer, vulvar and vaginal cancer caused by HPV 16 or HPV 16 or 18, genital warts caused by HPV 6 or 11, and lesions caused by HPV 6, 11, 16, or 18 (CIN 1-3, cervical carcinoma *in situ* and grades 2 and 3 vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN).

Young women should be vaccinated before their first sexual relation, since HPV infection is often acquired some months after. The vaccine should not be administered to pregnant women; the FDA classifies it as category B (animal studies have not shown danger for the fetus, although there are no controlled studies in pregnant women) (94).

Vaccines are not effective at preventing cervical disease if the woman is infected by a genotype carrying the vaccine. Nevertheless, previous PCR is not necessary, given that few women are infected by HPV 16 and 18 at the same time (95). Women with a history of genital warts and/or an abnormal cervical cytology can also be vaccinated, as they are unlikely to be infected by all the types contained in the vaccine.

In October 2006, the EMEA centrally authorized the HPV vaccine **Gardasil®**. In October 2007 in Spain, the Interterritorial Council of the National Health System approved the inclusion of the vaccination in the vaccination schedule for girls aged 11 to 14 years.

Prophylactic vaccines for HPV and HIV

One clinical trial has shown the efficacy and safety profile of the quadrivalent vaccine in HIV-infected men with good immunological status taking ART (96). CD4 lymphocyte count—both nadir and after administration of the vaccine—will determine the achievement and maintenance of protective antibody levels.

The efficacy of the quadrivalent vaccine has been shown to be similar in HIV-infected children and in non-HIV-infected children (97).

Therapeutic vaccines

Clinical studies indicate that prophylactic vaccines have no therapeutic effect; therefore, they cannot be applied in women with persistent HPV infection at risk of developing cervical cancer. Prophylactic vaccines do not provide protection against progression of CIN of a serotype present before vaccination. Consequently, millions of women already infected by HR-HPV would require treatment to help their immune system to control the infection. Therapeutic vaccines could be such a treatment.

The results of trials with therapeutic vaccines have generally been modest: some do not reveal a therapeutic response and others show partial regression of the lesions (98).

Therapeutic HPV and HIV vaccine

A recently published clinical trial evaluating the efficacy, tolerability, and immunogenic response of the therapeutic vaccine in HIV-infected MSM with a history of HPV infection and HPV lesions showed good tolerance and increased antibody to HPV 16 over 24 weeks; no improvement was observed in the results of anal histology or cytology, although no patients progressed to invasive cancer (99).

Table 1. Classification of the recommendations used in this document

Strength of the recommendation

Level A: Strong evidence to support the recommendation for use
Level B: Moderate evidence to support the recommendation for use
Level C: Insufficient evidence to support the recommendation

Quality of the recommendation

I: Evidence from at least 1 randomized clinical trial
II: Evidence from at least 1 well-designed nonrandomized clinical trial, from cohort or case-control studies (preferably from more than 1 center), or from time series, or dramatic results from uncontrolled experiments.
III: Evidence from opinions of respected authorities based on clinical experience or descriptive studies.

Table 2. Screening tests

	Baseline Visit	Follow-up Visit	
		No or sporadic risk practices	Previous STI and/or risk practices
Clinical history	+/+++	+	+++
Physical examination	+/+++	+	+++
Additional tests			
Serology	√	√	√
Microbiology			
Pharynx	√		√
Urethra	√		√
Vagina/Cervix			
Culture	√		√
Cytology*	√	√	√
Anal (cytology)**	√	√	√

*If not performed by a gynecologist
**If anal sex or positive HPV at another site

Table 3. Causes of urethritis and cervicitis

	Etiologic Agents	Diagnostic Tests
Gonococcal	*Neisseria gonorrhoeae*	Gram stain: intraleukocyte gramnegative diplococci Culture of urethral or cervical secretion: method of choice Serology (EIA): can be performed in urine DNA detection (PCR): if the culture is not available or sample transport is delayed
Nongonococcal	*Chlamydia trachomatis*, serotypes D-K (15%-55%) *Ureaplasma urealyticum* (10%-40%) *Mycoplasma genitalium* Other (20%-40%): *Trichomonas vaginalis* (4%), Herpes simplex, *Haemophilus* (especially in active anal sex), oropharyngeal flora (oral sex), noninfectious causes (trauma, autoimmune disease, allergic disease, and unknown agent in up to 25%)	Culture of urethral or endocervical sample: should always include epithelial cells Serology (direct immunofluorescence, EIA) DNA detection (PCR): should be performed in urine

Abbreviations: EIA, enzyme immunoanalysis; PCR, polymerase chain reaction.

Table 4. Treatment of urethritis and cervicitis

Gonococcal Etiology (All in Single Doses)	Nongonococcal Etiology (*Chlamydia*)
• Cefixime: 400 mg po • Ceftriaxone: 125-250 mg IM (A) • Cefuroxime axetil: 1 g po • Ciprofloxacin: 500 mg po (A)* • Ofloxacin: 400 mg po (A)* • Levofloxacin: 250 mg po* • Norfloxacin: 800 mg po* • Spectinomycin: 2 g IM (A) • Amoxicillin: 2-3 g + probenecid 1 g (B) • Azithromycin: 1-2 g po • Cefpodoxime proxetil: 400 mg po • Ceftibuten: 400 mg po	• Azithromycin: 1 g po in a single dose (A1a) • Doxycycline: 100 mg/12 h po x 7 d (A1a) • Erythromycin: 500 mg/6 h x 7 d (A) or 500 mg/12 h x 14 d (A1b) or 250 mg/6 h x 14 d • Minocycline: 100 mg/24 h po x 9 d (A) • Ofloxacin: 200 mg/12 h x 7 d (A1b) or 400 mg/24 h x 7 d (A1b) • Levofloxacin: 500 mg/24 h po x 7d

*The high frequency of quinolone-resistant gonococci advises against the use of this drug group as empiric therapy.
If the patient has followed the initial treatment and re-exposure can be ruled out, suspect uncommon causes of urethritis. The recommended regimen in such cases is metronidazole or tinidazole at 2 g po in a single dose (possibility of *Trichomonas*) combined with erythromycin at 500 mg/6 h po x 7 d (possibility of tetracycline-resistant *Ureaplasma urealyticum*). If symptoms persist after 2 cycles of antibiotic therapy, re-administering treatment to the partner and erythromycin (500 mg/6 h po x 3 wk) can prove useful (10,11).

Table 5. Vulvovaginitis

Diagnosis	**Normal Vagina**	**Vulvovaginitis by *Candida***	**Trichomoniasis**	**Vaginosis**
Flora	*Lactobacillus spp*. Scarce-moderate	*C. albicans* and other fungi	*Trichomonas vaginalis*	*Gardnerella vaginalis*, *Mycoplasma*, anaerobes
Symptoms	None	Irritation, pruritus, leukorrhea	Profuse and foul-smelling leukorrhea	Abundant and foul-smelling leukorrhea
Vaginal exudate	Clear or white, heterogeneous	White, in adherent aggregates	Yellowish, homogeneous, not very viscous, and foamy	White or grayish, homogeneous
Inflammation at the introitus (vagina/vulva)	No	Erythema of the vaginal epithelium, frequent dermatitis	Erythema of the vaginal epithelium, cervical petechiae	No
pH of the exudate	<4.5	<4.5	≥4.5	≥4.5
Amine (fishy) smell when KOH (10%) is added to the exudate	No	No	Frequently	Always
Microscopy	Epithelial cells. Predominant lactobacilli	Leukocytes, epithelial cells: yeasts, pseudomycelia in 80% of cases	Leukocytes, *Trichomonas* in 80-90% of symptomatic patients	Clue cells, scarce polymorphonuclear cells, lactobacilli, mixed flora
Approach to sexual partner	None	None. Topical therapy in cases of penile dermatitis	Investigate other STI. Metronidazole	Investigate other STI

Table 6. Treatment of trichomoniasis, candidiasis, and bacterial vaginosis

	Treatment of Choice	**Alternative Treatment**	**Pregnancy**	**Recurrence**
Trichomoniasis	• Metronidazole • Tinidazole Both at 2 g in single oral doses	• Metronidazole 500 mg/12 h x 7 d • Metronidazole gel (less effective)	Metronidazole 2 g in a single dose	Metronidazole 500 mg every 12 h x 7 d Tinidazole 2 g in a single dose If no cure, metronidazole or tinidazole 5 d If no improvement, evaluate sensitivity of *Trichomonas* to these agents
Candidiasis	• Clotrimazole 1% cream at 5 g/d x 7-14 d or 100 mg in 1 pessary/d x 7 d • Clotrimazole 100 mg 2 tab/3 d • Clotrimazole 500 mg 1 intravaginal tab • Miconazole 2% cream at 5 g intravaginally for 7 d or 100 mg as 1 pessary/d x 7 d	• Fluconazole 150 g po in a single dose	Topical imidazole 7 d	Topical imidazole derivatives (7-14 d) or fluconazole 100-150-200 mg every 3 d x 3 doses

Bacterial vaginosis	• Metronidazole 500 mg/12 h x 7 d • Metronidazole gel 0.75% at 5 g intravaginally/d x 5 d • Clindamycin 2% cream at 5 g intravaginally/d x 7 d	• Clindamycin 300 mg/12 h x 7 d • Clindamycin pessary 100 mg before bedtime	• Metronidazole 500 mg/12 h po x 7 d or 250 mg/8 h x 7 d • Clindamycin 300 mg/12 h x 7 d	Metronidazole gel 0.75% twice weekly for 6 months

Nursing mothers: suspend breastfeeding during administration of metronidazole or tinidazole until 12-24 hours after the last dose of metronidazole and 3 days after the last dose of tinidazole (8). Patients who are allergic to nitroimidazoles should undergo desensitization with metronidazole. Treatment with topical agents can be administered; however, the cure rate is lower.

Table 7. Sexually transmitted infections causing genital ulcer disease

Disease	Etiology	Incubation Period	Clinical Lesion	Regional Lymph Nodes	Diagnostic Tests
Chancroid	*Haemophilus ducreyi*	3-10 d	Single or multiple painful indented ulcers with a purulent base, soft margins.	Unilateral, fixed, and painful, with a tendency to fistulize	Culture
Primary syphilis	*Treponema pallidum*	2-4 wk	Single painless, indurated, nonpurulent ulcer	Bilateral, mobile, painless, hard	Dark-field microcopy,* serology
Genital herpes	HSV	3-7 d	Vesicles, superficial erosions, or painful ulcers; history of herpes	Bilateral, Mobile, painful, hard	Cell culture, PCR
Venereal lymphogranuloma	*Chlamydia trachomatis* L1-3	3-12 d	Transient indurated painless sore	Unilateral, painful, and with a tendency to fistulize	Serology, culture, PCR
Donovanosis	*Calymmatobacterium granulomatis*	2-12 wk	Reddish/flesh-colored colored chronic indurated ulcer	No lymphadenopathy, pseudo-buboes	

* Not valid in oral lesions

Table 8. Recommendations for treatment and follow-up of syphilis in HIV-infected patients

	Treatment of Choice	Alternative Treatment*	Follow-up
Primary, secondary, or early latent syphilis	Intramuscular benzathine penicillin G at 2,400,000 IU in a single dose[1]	• Doxycycline (100 mg/12 h x 2 wk) • Azithromycin (2 g in a single dose)[2]	Clinical and serological monitoring (nontreponemal tests) at 3, 6, 9, and 12 mo
Late latent syphilis, syphilis of unknown duration, tertiary syphilis	Intramuscular benzathine penicillin 2,400,000 IU/wk for 3 wk (days 0, 7, and 14)	• Doxycycline (100 mg/12 h x 4 wk • Azithromycin (500 mg/d x 10 d)[2]	Clinical and serological monitoring (nontreponemal tests) at 3, 6, 9, 12, and 24 mo
Neurosyphilis	Intravenous sodium penicillin G at 3-4 million IU every 4 h or 18-24 million IU in a continuous infusion, both for 10-14 d[3]	• Penicillin-allergic patients should undergo desensitization and subsequent treatment with penicillin • Intravenous ceftriaxone (2 g/d for 10-14 d)[4]	Evaluation of CSF every 6 mo until totally normal

***** In the case of penicillin-allergic patients, the alternatives have not been sufficiently evaluated to consider them first-line.

[1]Even though most HIV-infected patients respond to this treatment, some authors recommend adding 2 additional weekly doses of intramuscular benzathine G penicillin at 2,400,000 IU.

[2]Azithromycin is a useful therapeutic option for the treatment of primary and secondary syphilis. However, intrinsic resistance to this drug and failures are increasingly common.

[3]Some authors recommend a weekly dose of intramuscular benzathine penicillin at 2,400,000 IU for 3 weeks once the previous treatment has finished.

[4]Crossed hypersensitivity reactions may occur between the two.

Table 9. Types of HPV and associated diseases

HPV	Associated Diseases
16	More than 50% of high-grade CIN and carcinoma
18	10% of squamous cell carcinoma, 50% of adenocarcinoma, 90% of undifferentiated small cell squamous carcinoma
31,45	5-10% of CIN, squamous carcinoma
33, 39, 51, 55, 56, 58, 59, 68, m, m4, mm7, mm9	Less than 3% (each) of CIN, squamous carcinoma
6, 11, 40, 42, 54, 57, 66, 84	Low-risk subtypes, never detected in carcinoma
61, 62, 64, 67, 69 to 72, 81, cp6108, iso39	Insufficient data to determine risk

Table 10. Types of HPV according to their oncogenic potential

High-risk types (associated with cancer)
16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 68, 69, 82
Low-risk types (not associated with cancer)
6, 11, 40, 42, 43, 44, 54, 61, 72, 81

Table 11. 2001 Bethesda System

Result	Initials	Includes
Negative for intraepithelial lesions or malignancy		
		Microorganisms, reactive changes, atrophy, post-hysterectomy glandular cell status
Abnormal epithelial cells		
Squamous cells		
Atypical squamous cells	ASC	
ASC of unknown significance	ASC-US	
Cannot rule out HSIL	ASC-H	
Low-grade squamous epithelial lesion	LSIL	HPV, mild dysplasia, CIN1
High-grade squamous epithelial lesion	HSIL	Moderate and severe dysplasia, carcinoma in situ, CIN2 and CIN3
Squamous cell carcinoma		
Glandular cells		
Atypical glandular cells	AGC	
Atypical glandular cells of undetermined significance, possibly neoplastic	AGUS	
Endocervical adenocarcinoma in situ	AIS	
Adenocarcinoma		
Other		Endometrial cells in women aged >40 years

CIN, cervical intraepithelial neoplasia.

Table 12. Bethesda criteria for the evaluation and classification of anal biopsy and cytology

1. Normal. 2. Low-grade squamous intraepithelial lesion (LSIL) corresponding histopathologically to AIN 1. 3. High-grade squamous intraepithelial lesion (HSIL) that may be AIN 2, AIN 3, or carcinoma in situ. 4. Atypical squamous cells of undetermined significance (ASCUS). 5. Atypical squamous cells in which a high-grade lesion cannot be ruled out (ASC-H). 6. Insufficient sample, <200 nucleated cells on the slide. AIN 1/LSIL are benign lesions that tend to regress, whereas AIN 2-3 are potential precursors of anal cancer.

Table 13. Diagnostic tests

Cytology
Sensitivity: 30-87% (51% for CIN 3)
Specificity: 86-100%
Samples: remove excess mucous first
- Exudate of endocervix and exocervix together or separately
- Vaginal exudate: only when it is not possible to visualize or reach the cervix
- Perianal exudate
- Exudate of the anal canal

Report: follow Bethesda system
- Sample quality:
  - Suitable
  - Processed and examined, but unsuitable for evaluation
  - Unsuitable and rejected
- See Table 12 for the result of the cytology study.

Conventional (Papanicolaou): first technique approved by the FDA for population-wide cervical cancer screening.
Samples: take with a swab, which is turned 3 times anticlockwise, or with cytobrush, which is turned 3 times, combined with a spatula turned once in the cervical os. Extend the sample on a slide in a unidirectional smear so as not to alter cell morphology; if a cytobrush is combined with a spatula, extend both on the same slide.

- High percentage of unsatisfactory samples: 8%
- Requires observation by an expert, although the technique has been automated (AutoPap 300, NeoPath Inc.)
- Inexpensive

Liquid or monolayer (ThinPrep): Insert the sample into the preservative solution.

- Sampling with a brush doubles the number of cells.
- Artifacts and contaminants are eliminated during preparation.
- Significantly reduces unsatisfactory samples.
- Reduces observation time.
- No evidence on sensitivity compared with the Papanicolaou smear.
- Other diagnostic techniques (eg, hybrid capture assay or PCR) can be carried out on the same sample.
- High cost (4 times that of Papanicolaou per carcinoma detected).

COLPOSCOPY: Observation of the cervix with a speculum, magnifying lens, and bright light. This must be performed in the case of an abnormal cytology result or when signs or symptoms indicate cancer.

ANOSCOPY: Observation of the anal canal and margin, dentate line, and distal portion of the rectum with a proctoscope, magnifying lens, and bright light.
Should be performed in any patient with anal warts.

For both techniques (colposcopy and anoscopy):
When combined with cytology, NPV almost 100%.
Report: following the Barcelona 2002 classification of the Nomenclature Committee of the International Federation of Cervical Pathology and Colposcopy.

- Application of acetic acid 3%: acetowhite epithelium and vascular patterns are suggestive of dysplasia or carcinoma.
- Application of Lugol solution:
  - Mahogany-colored epithelium: normal
  - Yellowish epithelium: dysplasia

Not possible to identify invasion; therefore, biopsy is necessary in the case of images suggestive of high-grade lesions or invasive cancer.

HISTOLOGY (biopsy): gold standard for diagnosis of lesions caused by HPV. Always performed after identification of suspicious lesion in colposcopy or anoscopy.

IDENTIFICATION OF HPV

Absence of a standard panel makes it impossible to measure and compare sensitivity and specificity of different commercial techniques for the identification of HPV.

Sampling for identification of HPV:

After taking samples for cytology.
Before applying acetic acid or Lugol solution.
With cotton-wool or alginate swab with(out) physiological saline or with the device used in each system when included.
Do not use brushes for amplification techniques.
Women:
After removing excess mucous, rotate the swab on the lesion.
Men:
Rubbing or rotation with a Dacron swab after scraping with a file or filter paper to desquamate the cells
In the absence of a lesion, combined sample of the different genital anatomic regions.
With specific devices when available; if not, with cotton or alginate swab with (out) physiological saline.
Do not use a brush; the excess material could inhibit the reaction.
Conservation at room temperature 24-48 h (samples in preservative solution, up to 2-3 weeks), refrigerated for several weeks and for longer periods at –20ºC.

HYBRIDIZATION (hybrid capture assay, HC2, Digene): hybridization of HPV DNA using specific RNA probes, hybrid capture with antibodies and signal amplification.

Uses 2 sets of probes, one for HR-HPV 13 and the other for LR-HPV 5.

HR-HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68
LR-HPV: 6, 11, 42, 43, and 44

Does not identify specific genotypes.
Samples: exudates collected using a specific device, biopsies in transport medium, or brush specimens in preservative and liquid cytology preparations.
Can be automated.
Sensitivity: 1 pg of DNA or 100,000 copies of viral genome.

IMMUNOHISTOCHEMICAL STAINING with fluorescein-marked DNA probes.
The Benchmark Inform system (Ventana Medical Systems, Tucson, Arizona, USA) performs this process automatically.
Identifies HPV using 2 sets of probes (low and high risk).
Samples: tissue, conventional cytology, or fluid.

CONSENSUS PCR on region L1, which encodes a viral capsid protein
Sensitivity: 10 copies of DNA/million cells.
Identifies genotypes individually.
MY09/11: degenerate primers that amplify a 450-bp fragment.
- Low sensitivity for degraded or poorly conserved DNA
- Do not detect genotype 35
- The variant PGMY09/11 enhances sensitivity and spectrum

Primers GP5/GP6 o GP5+/GP6+: amplify a 150-bp fragment.
- More sensitive
- Do not detect genotype 52, second most common cause of cervical cancer in some countries.

Visualization and identification of genotypes using hybridization with specific probes (arrays).
- Linear Array HPV, Roche Molecular Systems, can identify 37 low- and high-risk genotypes by hybridization with probes immobilized on the solid phase
  - HR: 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 64, 66, 67, 68, 69, 70, 73, 82, 83, 84, and IS39
  - LR: 6, 11, 40, 42, 54, 55, 61, 62, 71, 72, 81, and CP6108

CLART HPV2, Genomica SAU, can identify 35 genotypes with low-density arrays.
- HR: 16, 18, 26, 31, 33, 35, 39, 43, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73, 85, and 89.
- LR: 6, 11, 40, 42, 44, 54, 61, 62, 71, 72, 81, 83, and 84

SPECIFIC PCR: Uses primers to identify a specific genotype or the oncogenes E6 and E7.
Sensitivity in femtograms and specificity close to 100%.
Viral integration studies
Detection of variants
Relative quantification
Templex HPV, Genaco Medical Products, detects, identifies, and semiquantifies in a single tube 25 genotypes of HPV (21 HR and 4 LR), using specific primers for oncogenes E6 and E7, with sensitivities ranging from 20 to 100 copies/reaction.
- HR-HPV: 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, and 82
- LR-HPV: 11, 6, 42, and 44

ISOTHERMAL ENZYMATIC AMPLIFICATION: Fluorescent reading on a liquid cytology monolayer.

Cervista HR HPV, Hologic, detects 14 HR-HPV jointly: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

Cervista HPV 16/18, Hologic, identifies both genotypes in positive samples.

SOLID-PHASE REVERSE HYBRIDIZATION: A mix of primers amplifies a 65-bp fragment of region L1 and identifies the genotypes by hybridization on cellulose strips.

SPF_{10}-INNO LiPA HPV, Labo Bio-Medical Products.

High sensitivity for paraffin-embedded tissues.

Excess sensitivity entails contamination problems; therefore, primers are usually replaced by consensus primers, with a loss of sensitivity.

AMPLIFICATION OF E6/E7 mRNA

Expression of these oncogenes is an independent prognostic factor: the greater the expression, the lower the survival.

Samples: tissues, conventional or liquid cytology

In-Cell, Invirion, can be automated.

Table 14. Summary of treatment options for high-grade anal lesions

Treatment	Indication				Advantages	Disadvantages
	Perianal condyloma	Perianal AIN 2-3	Intra-anal condyloma	Intra-anal AIN 2-3		
Liquid nitrogen	X	X	X		Inexpensive. Can be carried out in office	Pain, several visits. Limited disease
Trichloroacetic acid 85%*	X	X	X	X	Inexpensive. Can be carried out in office	Pain, several visits. Limited disease
Podophyllin	X				Self-administered	Pain/irritation Several visits Patient might leave smaller lesions untreated

Imiquimod	X	X	X	X	Self-administered	Pain/irritation Several visits Patient might leave smaller lesions untreated Less effective in men than in women Less effective in HIV-positive patients
Infrared coagulation	X	X	X	X	Can be carried out in office. Moderately extensive disease. Relatively inexpensive	Pain, bleeding, infection
Electrocautery	X	X	X	X	Can be carried out in office. Extensive disease	Pain, bleeding, infection
Cold scalpel excision	X	X	X	X	Extensive disease	Pain, bleeding, infection

*More effective in young patients, HIV-positive patients, and patients with a maximum of 2 lesions. A high proportion of patients with AIN 2-3 respond.

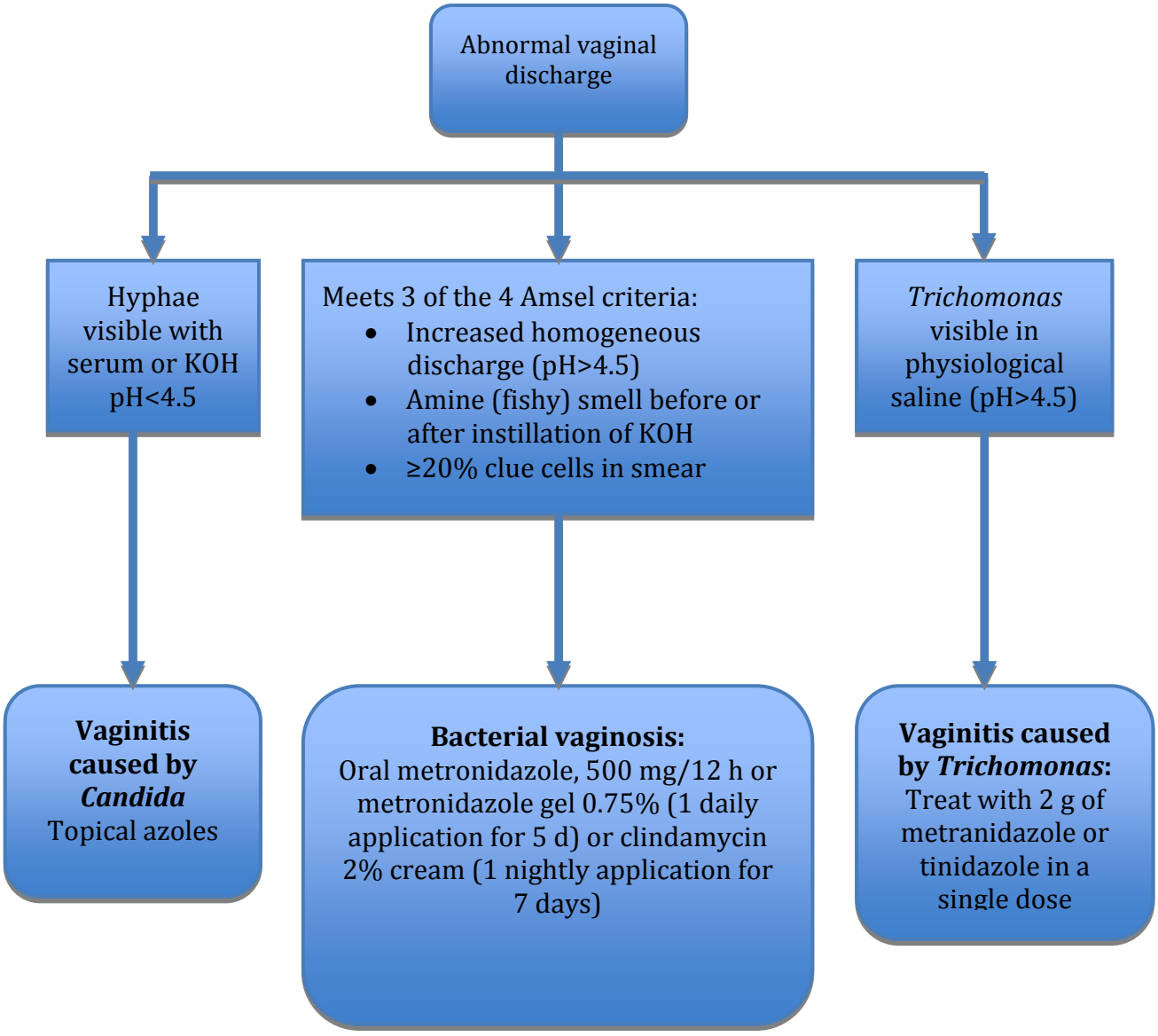


Figure 1. Algorithm for the diagnosis and treatment of abnormal vaginal discharge.

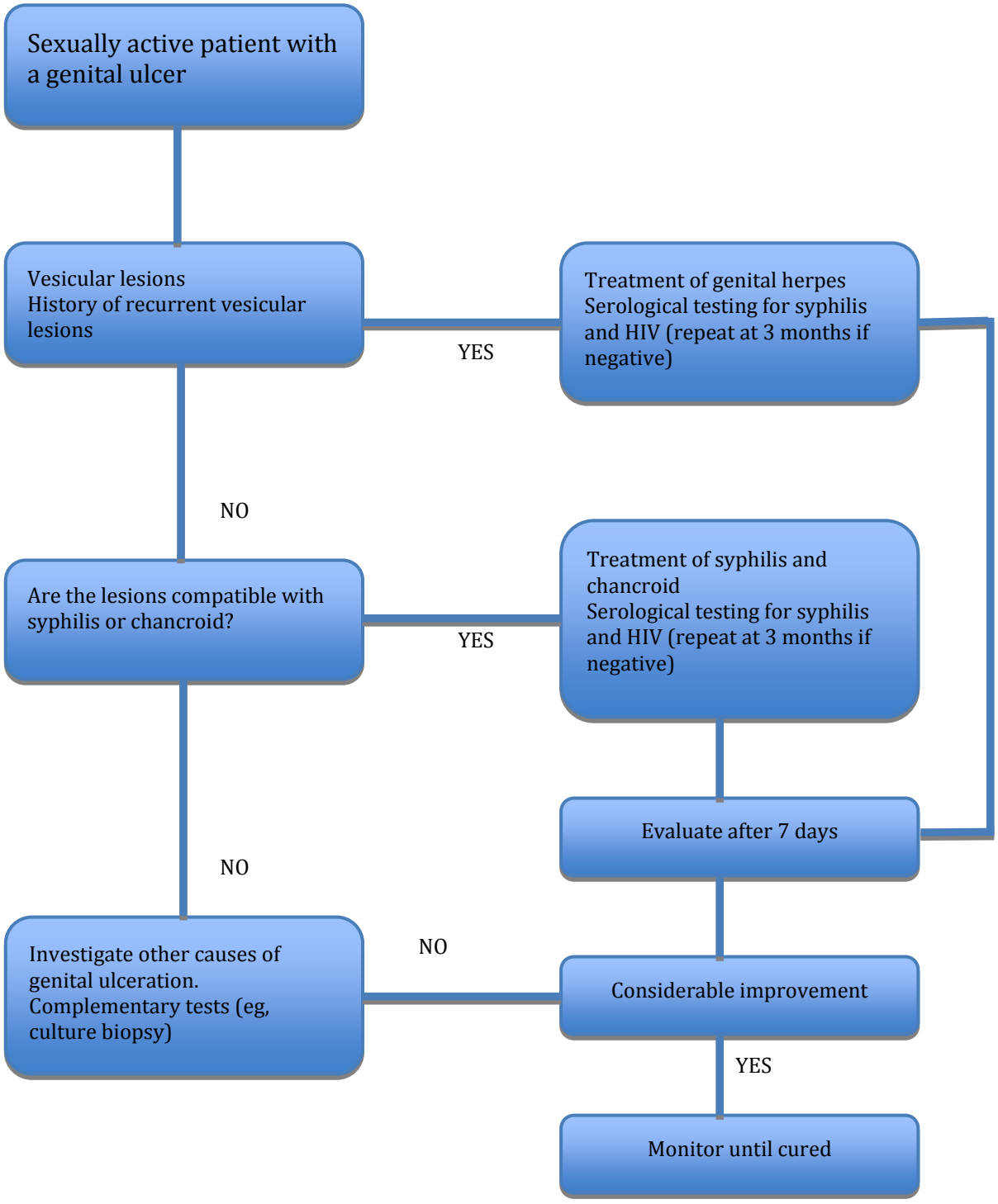
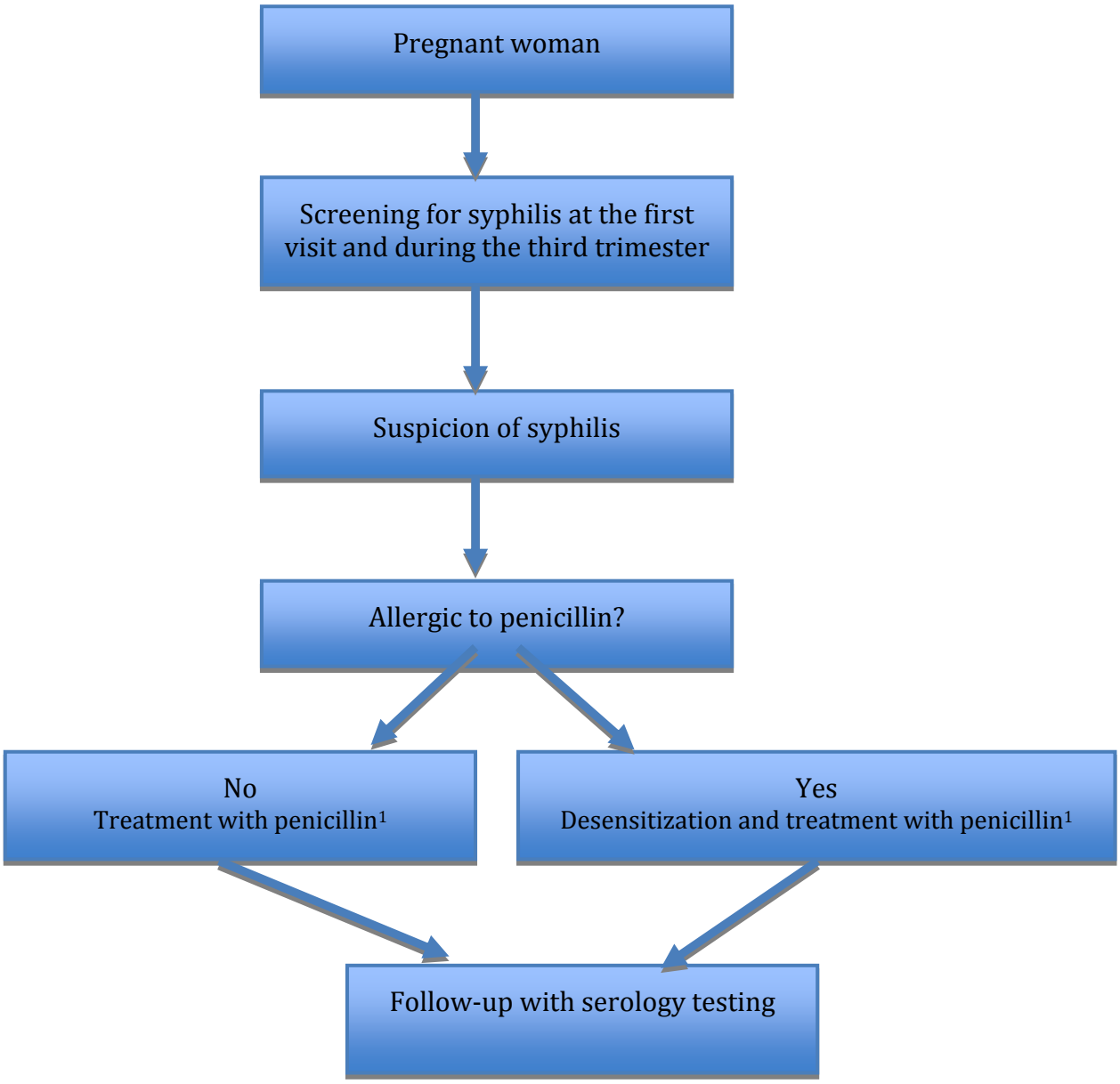


Figure 2. Algorithm for empirical treatment of genital ulcer disease.



[1]Diagnosis of early syphilis in the first or second trimester: intramuscular benzathine penicillin G 2,400,000 IU in a single dose. If the diagnosis is made in the third trimester: intramuscular benzathine penicillin G 2,400,000 IU in a single dose followed by an additional dose 1 week later. Although most HIV-infected patients respond to this treatment, some authors recommend that all HIV-infected patients have 2 additional weekly doses of intramuscular benzathine penicillin G 2,400,000 IU.

Figure 3. Management of syphilis in pregnant women.

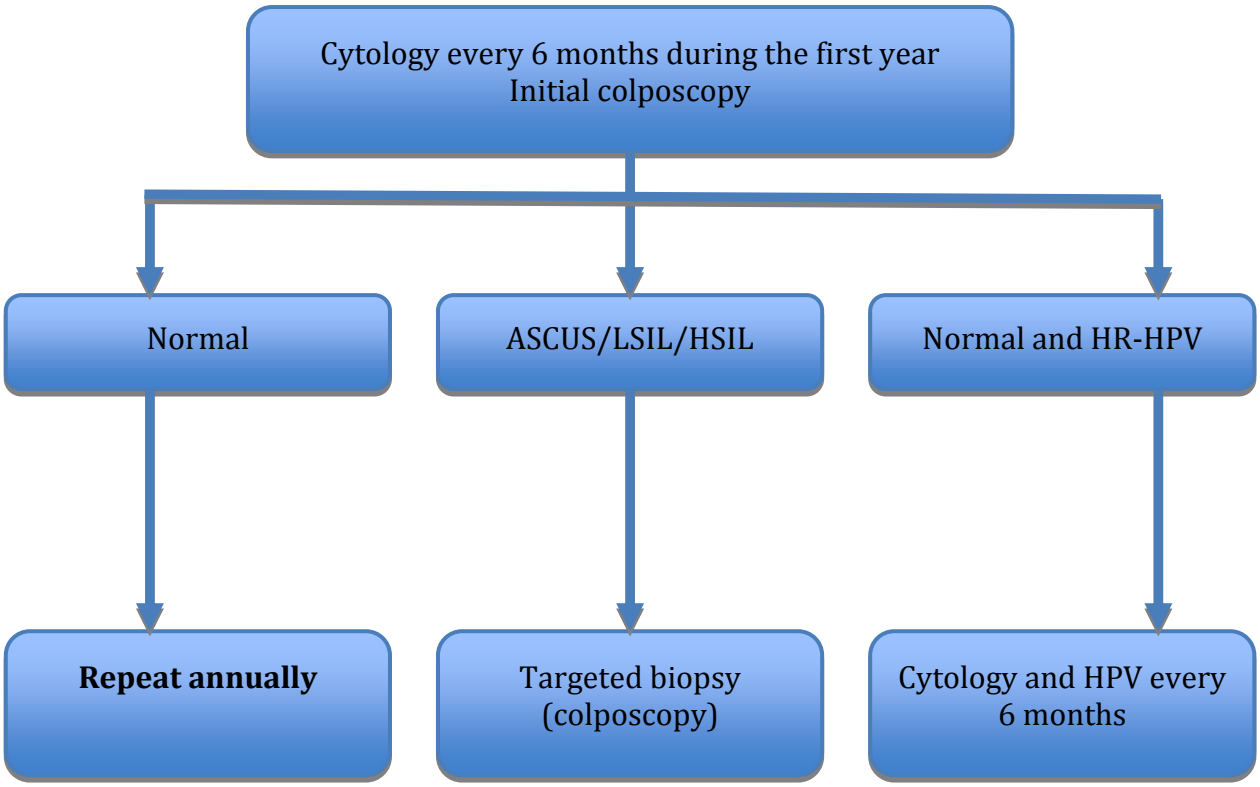


Figure 4. Algorithm for screening of cervical cancer.

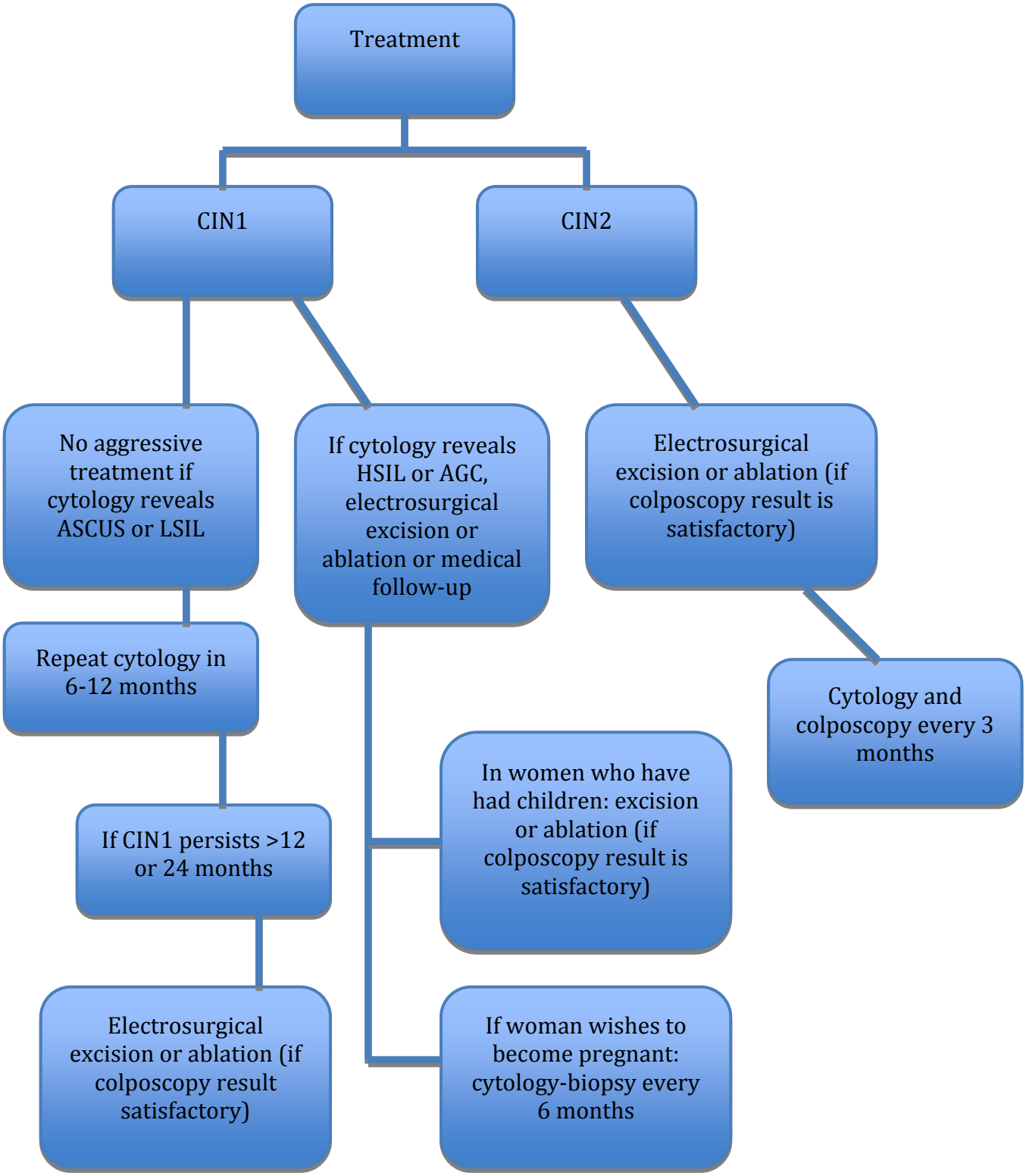


Figure 5. Algorithm for the treatment of CIN1-3.

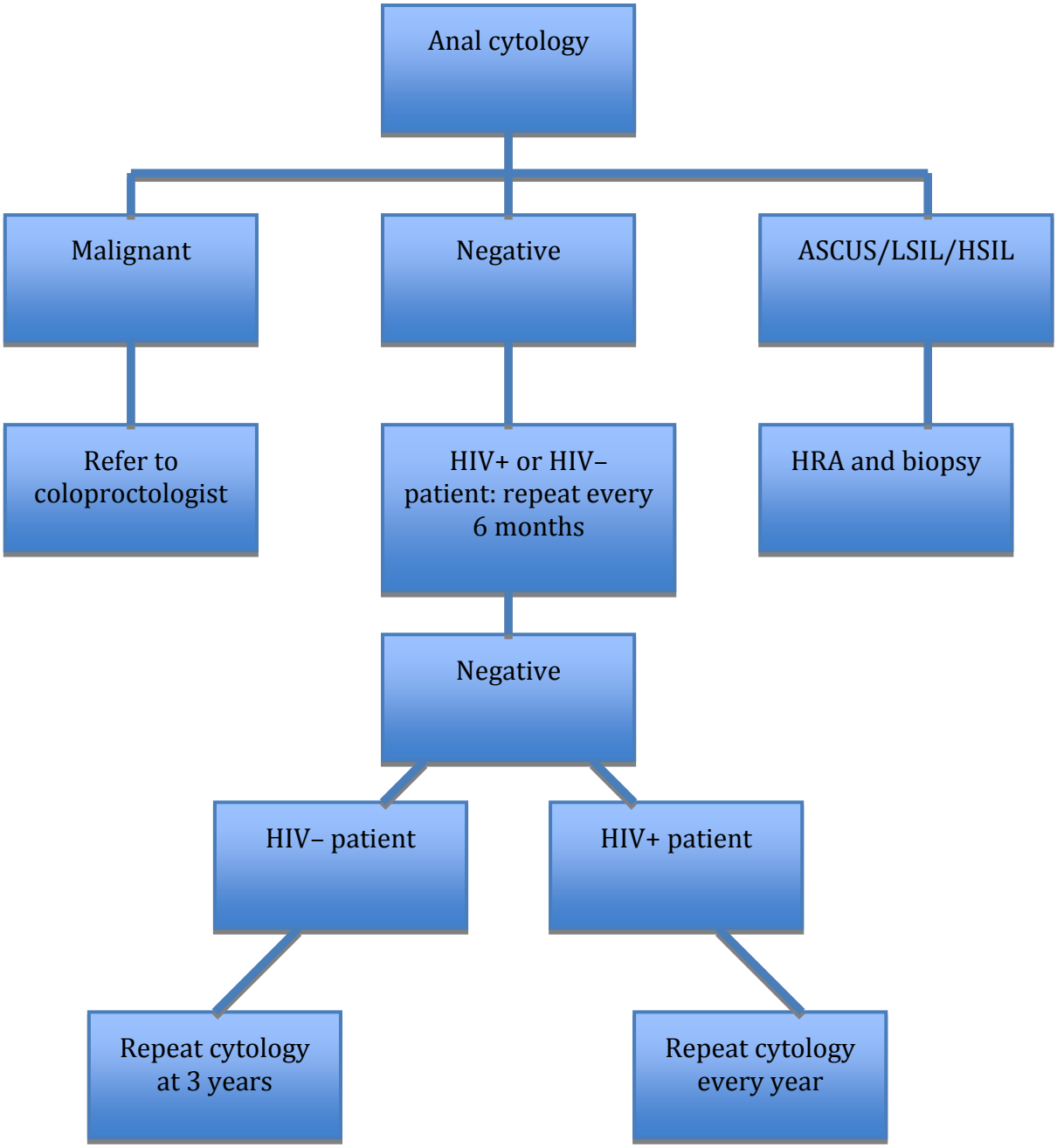


Figure 6. Algorithm for action to be taken according to the results of the annual cytology.

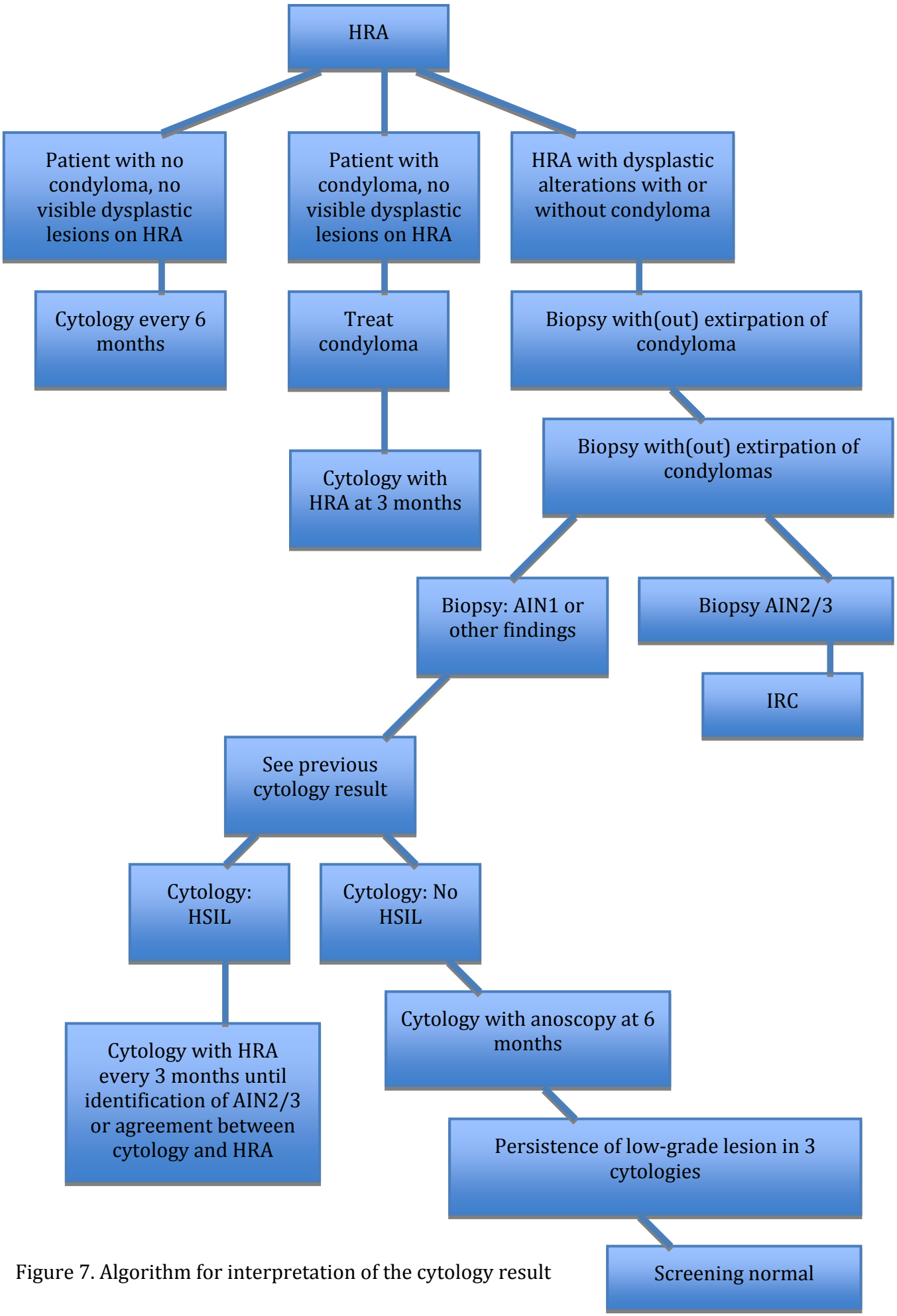


Figure 7. Algorithm for interpretation of the cytology result

References

1. Dougan S, Evans BG, Elford J. Sexually transmitted infections in Western Europe among HIV-positive men who have sex with men. Sex Transm Dis 2007;34:783-790.
2. Fenton KA, Imrie J. Increasing rates of sexually transmitted diseases in homosexual men in Western Europe and the United States: Why? Infect Dis Clin N Am 2005;19:311-331.
3. Rieg G, Lewis RJ, Miller LG, et al. Asymptomatic sexually transmitted infections in HIV-infected men who have sex with men: prevalence, incidence, predictors and screening strategies. AIDS Patient Care STDs 2008;22:947-954.
4. Aberg JA, Kaplan JE, Libman H, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV Medicine Association of Infectious Diseases Society of America. Clin Infect Dis 2009;49:651-681.
5. Ruiz-Sancho A, Barreiro P, Castellares C, et al. Outbreak of syphilis, but not of acute hepatitis C, among HIV-infected homosexual men in Madrid. HIV Clin Trials 2007;8:98-201.
6. Launay O, Grabar S, Gordien E, et al, for the HEPAVAc Study Group. Immunological efficacy of a three-dose schedule of hepatitis A vaccine in HIV-infected adults: HEPAVAC Study. J Acquir Immune Defic Syndr 2008;49:272-275.
7. Chun HM, Fieberg AM, Hullsiek KH, et al. Epidemiology of hepatitis B virus infection in a US cohort of HIV-infected individuals during the past 20 years. Clin Infect Dis 2010;50:426-436.
8. Hellín T, Rodríguez-Pichardo A, Ribera E. Enfermedades de transmisión sexual, 2ª ed. En Bouza E, coord. Protocolos Clínicos SEIMC. Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica; VIII Disponible en: http://www.seimc.org/protocolos/clinicos.htm
9. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. MMWR Recomm Rep 2006;55:1-94.
10. Bignell C; IUSTI /WHO. 2009 European (IUSTI/WHO) guideline on the diagnosis and treatment of gonorrhoea in adults. Int J STD AIDS 2009;20:453-457.
11. Shahmanesh M, Moi H, Lassau F, Janier M; IUSTI/WHO. 2009 European guideline on the management of male non-gonococcal urethritis. Int J STD AIDS 2009;20:458-464.
12. Hornes PJ. European guideline on epididymo-orchitis. Int J STD and AIDS 2001;12:88-93.
13. Ross J, Judlin P, Nilas L. European guideline for the management of pelvic inflammatory disease. IUSTI/WHO, 2008.
14. Holmes KK, Sparling PF, Mardh PA, et al. Genital Ulcer Adenopathy Syndrome. In: Ballard RC ed. Sexually Transmitted Diseases. New York: McGraw-Hill, 1999 p. 887-92.
15. Karthikeyan K. Recent advances in management of genital ulcer disease and anogenital warts. Dermatol Ther 2008;21:196-204.
16. Menéndez B, Ballesteros J, Clavo P, del Romero J. Aumento de la sífilis y de la infección gonocócica en varones homosexuales o bisexuales en Madrid. Med Clin (Barc) 2005;125:756.

17. Díaz A, Junquera ML, Esteban V, Martínez B, Pueyo I, Suárez J, et al. HIV/STI co-infection among men who have sex with men in Spain. Euro Surveill 2009; 14 pii:19426.
18. Palacios R, de la Fuente J, Murillas J, Nogueira JM, Santos J, por el Grupo de Estudio de Sida (GESIDA). Sífilis e infección por el virus de la inmunodeficiencia humana. Enferm Infecc Microbiol Clin 2006;24(supl.2):34-39.
19. European Union. European Centre for Disease Prevention and Control. http://ecdc.europe.eu.www.essti.org (Accessed March 5, 2010).
20. World Health Organization. Guías para el tratamiento de las enfermedades de transmisión sexual. 2004. http://whqlibdoc.who.int/publications/2005/9243546260.pdf. (Accessed March 5, 2010).
21. Koek AG, Bruisten SM, Dierdorp M, Van Dam AP, Templeton K. Specific and sensitive diagnosis of syphilis using a real-time PCR for *Treponema pallidum*. Clin Microbiol Infect 2006;12:1233-1236.
22. Lewis DA, Young H. Testing guidelines for individual sexually transmitted infections – syphilis. UK national screening and testing guidelines for sexually transmitted infections. Sex Transm Infect 2006;82:iv13–iv15.
23. Kingston M, French P, Goh B, et al; Syphilis Guidelines Revision Group 2008, Clinical Effectiveness Group. UK National Guidelines on the Management of Syphilis 2008. Int J STD AIDS 2008;19:729-740.
24. Ghanem KG, Moore RD, Rompalo AM, Erbelding EJ, Zenilman JM, Gebo KA. Lumbar puncture in HIV-infected patients with syphilis and no neurologic symptoms. Clin Infect Dis 2009;48:816-821.
25. Chan DJ. Syphilis and HIV: when a lumbar puncture is indicated. Curr HIV Res 2005;3:95-98.
26. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2009;58:1-207.
27. French P, Gomberg M, Janier M, Schmidt B, van Voorst Vader P, Young H. IUSTI: 2008 European Guidelines on the Management of Syphilis. Int J STD AIDS 2009;20:300-309.
28. Ghanem KG, Erbelding EJ, Wiener ZS, Rompalo AM. Serological response to syphilis treatment in HIV-positive and HIV-negative patients attending sexually transmitted diseases clinics. Sex Transm Infect 2007;83:97-101.
29. Rolfs RT, Joesoef MR, Hendershot EF, Rompalo AM, Augenbraun MH, Chiu M, et al. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. The Syphilis and HIV Study Group. N Engl J Med 1997;337:307-314.
30. Ghanem KG, Moore RD, Rompalo AM, Erbelding EJ, Zenilman JM, Gebo KA. Neurosyphilis in a clinical cohort of HIV-1-infected patients. AIDS 2008;22:1145-1151.
31. Koutsky L. Epidemiology of genital human papillomavirus infection. Am J Med 1997;102:3-8.
32. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer Statistics, 2009. CA Cancer J Clin 2009;59:225-249.

33. Muñoz N, Castellsagué X, de González AB, Gissmann L. Chapter 1: HPV in the etiology of human cancer. Vaccine 2006;24(Suppl3):S3/1-S3/10.
34. Bosch FX, Lorincz A, Muñoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol 2002;55:244-265.
35. Insinga RP, Liaw KL, Johnson LG, Madeleine MM. A systematic review of the prevalence and attribution of human papillomavirus types among cervical, vaginal, and vulvar precancers and cancers in the United States. Cancer Epidemiol Biomarkers Prev 2008;17:1611-1622.
36. Muñoz N, Bosch FX, de Sanjosé S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 2003;348:518-527.
37. Conant MA. Immunomodulatory therapy in the management of viral infections in patients with HIV infection. J Am Acad Dermatol 2000;43: S27-30.
38. Branca M, Costa S, Mariani L, et al. Assessment of risk factors and human papillomavirus (HPV) related pathogenetic mechanisms of CIN in HIV-positive and HIV-negative women. Study design and baseline data of the HPV-pathogenISS study. Eur J Gyneacol Oncol 2004;25:689-698.
39. From the Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. JAMA 1993;269:729-730.
40. Smith JS, Lindsay L, Hoots B, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. Int J Cancer 2007;121:621-632.
41. Crum-Cianflone NF, Huppler Hullsiek K, Marconi VC, et al. Anal cancers among HIV-infected persons: HAART is not slowing rising incidence. AIDS 2010;24:535-543.
42. Fox P. Anal cancer screening in men who have sex with men. Curr Opin HIV AIDS 2009,4:64-67.
43. Palefsky JM. Anal cancer prevention in HIV-positive men and women. Curr Opin Oncol 2009 ;21:433-438.
44. Berry M, Jay N, Cranston R, et al. Progression of high-grade anal intraepithelial neoplasia to invasive Session 154, poster number 867. In: 16th Conference on Retroviruses and Opportunistic Infections; 8–11 February 2009; Montreal, Canada.
45. Guiguet M, Boué F, Cadranel J, et al; on behalf of the Clinical Epidemiology Group of the FHDH-ANRS CO4 cohort. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies: a prospective cohort study. Lancet Oncol 2009;10:1152-1159.
46. Syrjänen KJ, Pyrhönen S, Syrjänen SM. Evidence suggesting human papillomavirus (HPV) etiology for the squamous cell papilloma of the paranasal sinus. Arch Geschwulstforsch 1983;53:77-82.
47. Xavier SD, Bussoloti FI, Lancelloti CL. Prevalence of histological findings of human papillomavirus (HPV) in oral and oropharyngeal squamous cell carcinoma biopsies: preliminary study. Braz J Otorhrinolaryngol 2005;71:510-514.

48. Herrero R, Castellsagué X, Pawlita M, et al; IARC Multicenter Oral Cancer Study Group. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. J Natl Cancer Inst 2003;95:1772-1783.
49. Goon P, Stanley M, Ebmeyer J, Steinsträsser L, et al. HPV and head and neck cancer: a descriptive update. Head Neck Oncol 2009;1:36.
50. Frisch M, Biggar RJ. Aetiological parallel between tonsillar and anogenital squamous-cell carcinomas. Lancet 1999;354:1442-1443.
51. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer Epidemiol Biomarkers Prev 2005;14:467-475.
52. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med 2007;356:1944-1956.
53. Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. J Natl Cancer Inst 2000;92:1500-1510.
54. Sirera G, Videla S, Pinol M, Canadas MP, Llatjos M, Ballesteros AL et al. High prevalence of human papillomavirus infection in the anus, penis and mouth in HIV-positive men. AIDS 2006;20:1201-1204.
55. Miralles-Guri C, Bruni L, Cubilla AL, Castellsagué X, Bosch FX, de Sanjosé S. Human papillomavirus prevalence and type distribution in penile carcinoma. J Clin Pathol 2009;62:870-878.
56. Gomousa M, Gialama E, Gomousas N, Gialama G. Genital human papillomavirus infection and associated penile intraepithelial neoplasia in males infected with human immunodeficiency virus. Acta Cytol 2000;44:305-309.
57. Kreuter A, Brockmeyer NH, Weissenborn SJ, et al. Penile intraepithelial neoplasia is frequent in HIV-positive men with anal dysplasia. J Invest Dermatol 2008;128:2316-2324.
58. Rombaldi RL, Serafini EP, Villa LL, et al. Infection with human papillomaviruses of sexual partners of women having cervical intraepithelial neoplasia. Braz J Med Biol Res 2006;39:177-187.
59. Castellsagué X, Bosch FX, Muñoz N, et al; International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. N Engl J Med 2002;346:1105-1112.
60. Nielson C, Schiaffino M, Dunne E, Salemi J, Giuliano A. Associations between male anogenital human papillomavirus infection and circumcision by anatomic site sampled and lifetime number of female sex partners. J Infect Dis 2009;199:7-13.
61. Madsen BS, van den Brule AJ, Jensen H, Wohlfahrt J, Frisch M. Risk factors for squamous cell carcinoma of the penis--population-based case-control study in Denmark. Cancer Epidemiol Biomarkers Prev 2008;17:2683-2691.
62. Boulet G, Horvath C, Vanden Broeck D, Sahebali S, Bogers J. Human papillomavirus: E6 and E7 oncogenes. Int J Biochem Cell Biol 2007;39:2006-2011.

63. The 2001 Bethesda System. Terminology for reporting results of cervical cytology. JAMA 2002;287:2114-2119.
64. Aubin F, Pretet JL, Jacquard AC, et al. Human papillomavirus genotype distribution in external acuminata condylomata: a Large French National Study (EDiTH IV). Clin Infect Dis 2008;47:610-615.
65. Brown DR, Schroeder JM, Bryan JT, Stoler MH, Fife KH. Detection of multiple human papillomavirus types in condylomata acuminata lesions from otherwise healthy and immunosuppressed patients. J Clin Microbiol 1999;37:3316-3322.
66. Carusi DA, Garner E. Treatment of vulvar and vaginal warts. UpTodate 17.3.
67. Bryan JT, Stoler MH, Tyring SK, McClowry T, Fife KH, Brown DR. Highgrade dysplasia in genital warts from two patients infected with the human immunodeficiency virus. J Med Virol 1998;54:69-73.
68. Robinson WR. Screening for cervical cancer in HIV infected women. UpToDate 17.3
69. Palefsky JM. Human papillomavirus-associated anogenital neoplasia and other solid tumors in human immunodeficiency virus-infected individuals. Curr Opin Oncol 1991;3:881-885.
70. Holschneider CH. Cervical intraepithelial neoplasia: Management. UpToDate 17.3.
71. Robinson WR. Preinvasive and invasive cervical neoplasia in HIVinfected women. UpToDate 17.3.
72. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ. Am J Obstet Gynecol 2007;197:340-345.
73. Schwartz LB, Carcangiu ML, Bradham L, Schwartz PE. Rapidly progressive squamous cell carcinoma of the cervix coexisting with human immunodeficiency virus infection: clinical opinion. Gynecol Oncol 1991;41:255-258.
74. Ahdieh-Grant L, Li R, Levine AM, et al. Highly active antiretroviral therapy and cervical squamous intraepithelial lesions in human immunodeficiency virus-positive women. J Natl Cancer Inst 2004;96:1070-1076.
75. Sirera G, Videla S, López-Blázquez R, Llatjos M, et al. Highly active antiretroviral therapy and incidence of cervical squamous intraepithelial lesions among HIV-infected women with normal cytology and CD4 counts above 350 cells/mm3. Antimicrob Chemother 2008;61:191-194.
76. Whitlow CB, Gottesman L. Sexually transmitted diseases. In: Wolff BG, Fleshman JW, Beck DE, Pemberton JH, Wexner SD eds. 1 edn. Chapt 12. New York: Springer, 2007:256-268.
77. Ho KS, Cranston RD. Anal cytology screening in HIV-positive men who have sex with men: what's new and what's now? Curr Opin Infect Dis 2010;23:21-25.
78. Pantanowitz L, Dezube BJ. The anal Pap test as a screening tool. AIDS 2010;24:463-465.
79. British HIV Association guidelines: HIV associated malignancies; 2008 pp. 60-61. Available at www.bhiva.org

80. Berry JM, Palefsky JM, Jay N, Cheng SC, Darragh TM, Chin-Hong PV. Performance characteristics of anal cytology and human papillomavirus testing in patients with high-resolution anoscopy-guided biopsy of highgrade anal intraepithelial neoplasia. Dis Colon Rectum 2009;52:239-247.
81. Bean SM, Chhieng DC. Anal-rectal cytology: A review. Diagn Cytopathol 2009;38:538-546. DOI 10.1002/dc
82. Pineda CE, Welton ML. Controversies in the management of anal highgrade squamous intraepithelial lesions. Minerva Chir 2008;63:389-399.
83. Siekas LL, Aboulafia DM. Establishing an anal dysplasia clinic for HIV-infected men: initial experience. AIDS Read 2009;19:178-186.
84. Backes DM, Kurman RJ, Pimenta JM, Smith JS. Systematic review of human papillomavirus prevalence in invasive penile carcinoma. Cancer Causes Control 2009;20:449-457.
85. Van der Snoek EK, Nieters HG, Mulder PG, van Doornum GJ, Osterhaus AD et al. Human paillomavirus infection in men who have sex with men participating in a Dutch gay-cohort study. Sex Trans Dis 2003;30:639-644.
86. Villa LL, Costa RL, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6,11,16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol 2005;6:271-278.
87. Garland SM, Hernández-Avila M, Wheeler CM. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007;356:1928-1943.
88. Paavonen J, Jenkins D, Bosch FX, et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. Lancet 2007;369:2161-2170.
89. Reisinger KS, Block SL, Lazcano-Ponce E, et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. Pediatr Infect Dis J 2007;26:201-209.
90. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915-1927.
91. Joura EA, Leodolter S, Hernández-Avila M, et al. Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials. Lancet 2007;369:1693-1702.
92. Markowitz LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2007;56(RR-2):1-24.
93. Product approval information: human papillomavirus quadrivalent (types 6, 11, 16, 18) vaccine, recombinant. Silver Spring, MD: Food and Drug Administration, 2008. (Accessed June 22, 2009, at http://www.fda.gov/cber/products/gardasil.htm.)

94. Garland SM, Ault KA, Gall SA, et al. Pregnancy and infant outcomes in the clinical trials of a human papillomavirus type 6/11/16/18 vaccine: a combined analysis of five randomized controlled trials. Obstet Gynecol 2009;114:1179-1188.
95. Wright TC Jr, Huh WK, Monk BJ, Smith JS, Ault K, Herzog TJ. Age considerations when vaccinating against HPV. Gynecol Oncol 2008;109(Suppl2):S40-S47.
96. Wilkin TJL, Goldstone S, Stier E, Berry M, Aboulafia D, Cohn D, et al. Safety and immunogenicity of the quadrivalent HPV vaccine in HIV-infected men: primary results of AIDS Malignancy Consortium Trial 052.
17th Conference on Retroviruses and Opportunistic Infection, San Francisco, February 16-19 2010. Abstract No. 1015.
97. Weinberg A, Song LY, Handelsman E, et al, and IMPAACT P1047 Team. Safety and immunogenicity of a quadrivalent vaccine to prevent human papilloma virus infection in HIV-infected children: IMPAACT P1047. 15th Conference CROI 2008, Boston 3-6 February. Poster 619.
98. Trimble CL, Frazer IH. Development of therapeutic HPV vaccines. Lancet Oncol 2009;10:975-980.
99. Anderson JS, Hoy J, Hillman R, et al. A randomized, placebo-controlled, dose-escalation study to determine the safety, tolerability, and immunogenicity of an HPV-16 therapeutic vaccine in HIV-positive participants with oncogenic HPV infection of the anus. J Acquir Immune Defic Syndr 2009;52:371-381.