Gynaecological care of the HIV patient

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It is estimated that every day in sub-Saharan Africa approximately 5 500 women are newly infected with HIV and more than 3 000 die from AIDS-related illnesses. In this region, where women comprise 58% of the existing HIV-positive patients, infection is increasing faster among women than among men. Among young people aged 15 - 24 years, women are 2.5 times more likely than men to be infected by HIV. In southern Africa, HIV infection is transmitted overwhelmingly through heterosexual contact and is more likely to occur from seropositive male to seronegative female than from seropositive female to seronegative male. Risk factors for the transmission of HIV are shown in Table I.

Table I. Risk factors for transmission of HIV

- Sexually transmitted diseases
- Lack of condom use
- Low CD4 or high viral load in infected partner
- Genital ulcers
- Sex during menses
- Multiple sexual contacts
- Traumatic sex (dry sex)
- Anal intercourse
- Uncircumcised male

Gynaecological diseases are commonly encountered in HIV-infected women, with the likelihood of the condition being more common and more severe the greater the immunosuppression. Conditions that may arise include vaginal and cervical infections, lower genital tract neoplasia, pelvic inflammatory disease, menstrual irregularities, aspects pertaining to contraception and reproductive options.

VAGINAL AND CERVICAL INFECTIONS

Recent studies have shown no significant differences in the prevalence of Chlamydia trachomatis, Neisseria gonorrhoeae, bacterial vaginosis or trichomoniasis in HIV-seropositive compared with HIV-seronegative women. Of these infections, bacterial vaginosis appears to be the most common, occurring in approximately 35% of women, regardless of HIV status. The association between HIV infection and vaginal candidiasis has been debated in the past, although again, recent studies have not demonstrated an increased incidence except in severely immunocompromised women with CD4 counts of < 200 cells/mm$^3$. This seems to apply to both Candida albicans and non-C. albicans species. The treatment principles for managing vulvovaginal candidiasis are identical to those used in HIV-negative women. These include topical antifungal agents such as clotrimazole, miconazole and terconazole. Single-dose fluconazole for treatment of acute episodes should be used sparingly because fluconazole resistance has been described. In the event of recurrent vulvovaginal candidiasis, topical antifungal therapy should be extended to 10 - 14 days. If there is no response, then oral fluconazole, 150 mg daily for 14 days or 150 mg weekly long-term, should be given. Boric acid suppositories, 600 mg twice daily for 2 weeks, can be considered in women with azole-resistant infections and particularly so for women infected with C. glabrata species.

The decision to use long-term fluconazole must be carefully considered so as to avoid development of resistance and the negligible incidence of serious invasive disease. Immunosuppression can have an impact on the severity

HIV is probably the most important infection among young women in sub-Saharan Africa.
or frequency of the disease. Other options for management of vaginal and cervical infections are shown in Table II. These infections could influence HIV transmission by altering HIV shedding, increasing inflammatory cells in the cervical or vaginal epithelium or by adverse effects on protective vaginal microflora and therefore should be treated.

**GENITAL ULCERATIVE DISEASE**

Genital ulcers seen in HIV-infected women can be large, necrotic, very painful and may be difficult to diagnose. They are commonly seen in severely immunocompromised women. Approximately 50% will be idiopathic and are called aphthous ulcers, while the rest have an infectious origin of which the herpes simplex virus, mixed bacteria, syphilis, *Haemophilus ducreyi*, mycobacteria and cytomegalic viruses are the commonest. These ulcers commonly reflect failure to respond to antiretroviral therapy. Approximately 40% of these women will also have ulceration of the oral cavity.

The recommended diagnostic approach is outlined in Table III. Treatment requires individualisation based on results obtained, but the fundamental priority is highly active antiretroviral treatment (HAART). Ideally, treatment other than HAART should await culture and biopsy results, but presumptive treatment with valacyclovir can be initiated. Individual appropriate therapy can then be added, but the addition of Sitz baths twice daily, antibiotics for secondary vaginal infections and adequate analgesics should also form part of management. If no aetiological factor is found, HAART is the option of choice with or without valacyclovir. Aphthous ulcers not responsive to any conventional therapies may respond to thalidomide 200 mg daily for 14 days.

**Syphilis**

Syphilis is seen more commonly than any other STD at the time of diagnosis of HIV, and all patients with syphilis should have HIV testing, with a retest after 3 months, if the first HIV test is negative for those at high risk. Serological tests for syphilis may be altered by HIV-induced immunosuppression with both false-positive and false-negative serological tests being described. HIV-infected women with primary syphilis are more likely than HIV-negative women to have multiple chancres at initial presentation and genital ulcers with secondary syphilis.

HIV-infected women with clinical findings consistent with primary syphilis, but with negative testing, should receive empiric treatment. Treatment of syphilis in HIV-infected individuals is similar to that in the general population, but women with latent syphilis or syphilis of unknown duration should undergo examination of their cerebrospinal fluid prior to therapy, although routine lumbar puncture is not recommended in the absence of serological failure or neurological features. After treatment, serological evaluation should take place at 3, 6, 9, 12, and 24 months to confirm treatment response.

**Chancroid**

HIV-positive women who have chancroid may require more prolonged therapy to avoid treatment failure when compared with HIV-negative women. Single-dose treatment probably should be avoided, especially if the woman is immunosuppressed and follow-up cannot be ensured. Follow-up examination 3 - 7 days after initial treatment is important, and further treatment should be administered if necessary.

See Table IV for treatment options for syphilis, HSV and chancroid.

**Table II: Treatment options for vaginal and cervical infections**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Candidiasis</strong></td>
<td>- Miconazole suppository 200 mg x 3 days</td>
</tr>
<tr>
<td></td>
<td>- Miconazole 2% vaginal cream x 7 days</td>
</tr>
<tr>
<td></td>
<td>- Clotrimazole vaginal cream 1% x 7 - 14 days</td>
</tr>
<tr>
<td></td>
<td>- Clotrimazole tabs 100 mg daily for 7 days or 500 mg stat</td>
</tr>
<tr>
<td><strong>Trichomoniasis</strong></td>
<td>- Metronidazole 2 g orally</td>
</tr>
<tr>
<td><strong>Bacterial vaginosis</strong></td>
<td>- Metronidazole 500 mg orally bd x 7 days</td>
</tr>
<tr>
<td><strong>Chlamydia trachomatis</strong></td>
<td>- Doxycycline 100 mg bd x 7 days</td>
</tr>
<tr>
<td></td>
<td>- Azithromycin 1 g or 2 g stat</td>
</tr>
</tbody>
</table>

**HSV infections**

HSV infections are more common in HIV-positive women due to increased viral shedding, especially if associated with severe immunosuppression. They have a most atypical presentation, the infection appearing as flat lesions with evidence of secondary bacterial infection. They are particularly refractory in nature or long-lasting – in fact, HSV lasting longer than 1 month suggests immunodeficiency and is an AIDS-defining illness.

Ulcers due to HSV have a strong association with the sexual transmission of HIV, a concept underscoring the need to counsel HIV-positive women to use barrier methods during every act of intercourse. Treatment for HSV infection is similar to that in non-infected women for episodic infections and is only slightly modified to include higher doses for recurrent or suppressive therapy. Long-term use of acyclovir as suppressive therapy for up to 10 years has been shown to be effective and safe. Acyclovir-resistant HSV may be encountered in 11 - 17% of HIV-infected women, and in these valacyclovir, famciclovir, foscarnet or cidofovir may need to be considered. The HSV lesions may present and recur frequently on the labia majora, labia minora, and less commonly on the sacrum or buttocks.
Both HIV and the organisms responsible for pelvic inflammatory disease (PID) are sexually transmitted and it is not uncommon for both conditions to coincide. HIV may alter the clinical course of PID in that HIV-positive women with PID have higher temperatures, lower white blood cell counts, more syphilis, more bacterial vaginosis, less chlamydia, and less abdominal tenderness compared with HIV-negative women. Tubo-ovarian abscess formation is twice as common, but four times more common in those with a CD4 count < 200 cells/mm³. Therefore, more surgical intervention is required.

The microbiology of PID is very similar to that found in HIV-negative women, although there may be a higher percentage of streptococcus and mycoplasma species. Antibiotic regimens with strong anaerobic coverage can be used initially in less complicated cases, although patients may take longer to recover totally. The Centers for Disease Control (CDC) recommends that all HIV-infected women with PID should be managed as inpatients and given parenteral therapy. Most clinicians maintain a low threshold to hospitalise and treat these patients with intravenous antibiotics if the HIV disease is advanced. See Table V & VI for outpatient and inpatient therapy for PID in HIV-infected women. These tables reflect primarily the CDC recommendations.

HIV-infected women have a 5 - 6-fold increased risk of developing squamous intraepithelial neoplasia compared with HIV-negative women. Human papillomavirus infection, overwhelmingly the most potent aetiological factor in cervical cancer, is more common in HIV-infected women in terms of prevalence, acquisition and persistence. Severe immunosuppression (CD4 < 200 cells/mm³) and high viral load increase the likelihood of HPV infection, abnormal smears and squamous intraepithelial lesions (SIL). Approximately 20% of HIV-infected women, as opposed to 3 - 5% of HIV-negative women, will develop SIL on cervical screening. In addition, the occurrence of atypical squamous cells of undetermined significance (ASCUS) is also markedly increased.

Screening for cervical cancer is of paramount importance in the HIV-infected woman. Importantly, the sensitivity and specificity of the cervical smear in HIV-infected women has been reported to be similar to that in HIV-negative women. Ideally, the smear should be repeated twice in the first year after diagnosis of HIV, and if the results of the smear are normal, annually thereafter. Indications for colposcopy would be similar to those that dictate its need in the HIV-negative woman. Routine colposcopy is not recommended. In HIV-infected women mild cytological atypia and inflammation on the cervical smear are more frequently associated with dysplasia. Hence the recommendation that colposcopic examination is warranted after a single Pap smear showing cytological atypia (ASCUS, low-grade SIL or high-grade SIL, atypical glandular cells of undetermined significance (AGUS)) and may even be warranted after a single smear showing severe inflammation that has not resolved after disease-specific treatment (i.e. for Neisseria gonorrhoeae, Chlamydia trachomatis, HSV or Trichomonas vaginalis).

### Table III. Diagnostic approach to the patient with genital ulcerative disease

- Swabs of ulcer or vaginal discharge for MC & S
- Serological tests for syphilis
- Culture for HSV and cytomegalovirus
- Acid-fast bacillus smear and mycobacterial cultures
- Tissue biopsy for MC & S and histology

### Table IV. Treatment of syphilis, HSV and chancroid

- **Syphilis**
  - Benzathine penicillin G, 2.4 MU IMI stat
  - Benzathine penicillin G, 2.4 MU IMI weekly x 3
  - Aqueous penicillin G, 18 - 24 MU daily x 10 - 14 days
- **HSV**
  - Acyclovir 200 mg 5x/day x 7 - 10 days
  - Famciclovir 250 mg 3x/day x 7 - 10 days
  - Valacyclovir 1 g 2x/day x 7 - 10 days
- **Severe HSV**
  - Acyclovir 800 mg 5x/day x 5 - 7 days
- **Refractory HSV**
  - Acyclovir 5 - 10 mg/kg IVI 8 hrly x 7 - 10 days
  - Valacyclovir 1g orally 2x/day x 7 - 10 days
- **Chancroid**
  - Azithromycin 1 - 1.2 g daily x 7 days
  - Erythromycin 500 mg 3x/day x 7 days

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Table V. **Outpatient therapy for PID in HIV-infected women**

Ofloxacin 400 mg po bd x 14 days  
Levofloxacin 500 mg po qid x 14 days  
Metronidazole with 500 mg po bd x 14 days

or

Ceftriaxone 25 mg IM x 1  
Cefoxitin 2 g IM x1  
Ciprofloxacin 500 mg po x 1

with

Probenecid 1g po stat

with

Metronidazole 500 mg po bd x 14 days  
Doxycycline 100 mg po bd x 14 days

or

Erythromycin 500 mg po qid x 14 days

Table VI. **Inpatient therapy for PID in HIV-infected women**

1. Cefotaxan 2 g IV 12 hrly or cefoxitin 2 g IV 6 hrly

   with

   Doxycycline 100 mg po/IV bd

   or

2. Clindamycin 900 mg IVI 8 hrly plus gentamycin 2 mg/kg IV or IM loading dose, then 1.5 mg/kg 8 hrly

   or

   Ofloxacin 400 mg IV 12 hrly or levofloxacin 500 mg IV 6 hrly

   plus

   Metronidazole 500 mg IV/rectally 8 hrly

   or

3. Ampicillin 3 g IVI 6 hrly

   plus

   Doxycycline 100 mg po/IV 12 hrly

   plus

   Gentamycin 2 mg/kg IV or IM loading dose, then 1.5 mg/kg 8 hrly

After clinical improvement, oral doxycycline 100 mg bd or oral clindamycin 450 mg qid to complete 14-day treatment course
Gynaecological diseases are commonly encountered in HIV-infected women, with the likelihood of the condition being more common and more severe the greater the immunosuppression.

The decision to use long-term fluconazole must be carefully considered so as to avoid development of resistance and the negligible incidence of serious invasive disease.

Ulcers due to HSV have a strong association with the sexual transmission of HIV, a concept underscoring the need to counsel HIV-positive women to use barrier methods during every act of intercourse.

Vulvar, vaginal and anal intraepithelial neoplasia (AIN) appear to be prevalent among HIV-infected women. The greater the immunosuppression, the greater the likelihood of AIN. Although vulvar, vaginal and anal cancers are infrequently reported in HIV-infected women, these may become more common as improved medical treatment of HIV leads to women living with immunosuppression and intraepithelial neoplasia for longer periods of time. Treatment of vulvar, vaginal or anal intraepithelial neoplasia is difficult because of the higher likelihood of recurrence after excisional or ablative therapy. Nevertheless, all HIV-infected women should have a careful inspection of the vulva and peri-anal region during pelvic examination, without or following application of 5% acetic acid to the vulva for 5 minutes and using low-power magnification. Any abnormality mandates colposcopy and biopsy. Currently it is unclear how HAART affects genital neoplastic disease. On the one hand it would be expected to decrease SIL by restoring immunocompetence, while on the other, it could increase SIL by prolonging life and increasing the exposure time to HPV. In reality, this has not been answered, with current studies showing very contradictory results and no definite trend.

Treatment of SIL in HIV-infected women, as in HIV-non-infected women, must take cognisance of the fact that cervical intraepithelial neoplasia (CIN) 1 has a low rate of progression to CIN 2 or 3. Despite any of the conventional methods of management, treatment of CIN 1 has a high failure rate in HIV-infected women. An option of treatment is only to observe CIN 1 lesions provided the CD4 is >200 cells/mm³ and if the woman will commit to follow-up appointments, which will allow treatment if there is any progression of the lesion. Cryotherapy is appropriate for CIN 1 if the CD4 count is <200 cells/mm³ or the patient is non-compliant.

In the case of CIN 2 or 3, ablative or excisional procedures are the treatment of choice. Cryotherapy is appropriate for CIN 2 or 3 if there is a satisfactory colposcopy result and no prior cervical treatment, and if the lesion is completely visible, <2 cm in diameter, and affecting no more than 2 quadrants. Cold knife cone biopsy should be reserved for high-grade lesions where malignancy is detected on Pap smear and micro-invasive disease or glandular lesion is present. Topical application of 5-fluorouracil may also be a useful adjuvant after excisional or ablative treatment of CIN 2 or 3. Excessive bleeding and cervical vaginal infection after cone biopsy or laser ablation are potential complications.

Second or third therapeutic procedures to manage CIN 2 or 3 are often required, although hysterectomy is not advocated as there is a 50% recurrence rate at the vaginal cuff. Following treatment, Pap smears need to be performed 6 monthly for 2 years because 90% of recurrences occur in this time. After 3 consecutive negative Pap smears, the patient can have an annual evaluation.

**INVASIVE CERVICAL CANCER**

In 1993, the CDC included invasive cancer of the cervix as an AIDS-defining illness. Whereas the relationship between SIL and HIV infection has been shown, a clear relationship between HIV infection and invasive cervical cancer has not been established in developing countries, even though this association appears to exist in Europe and the USA. Although there has been an increase in the background prevalence of HIV infection in the South African population and in patients with cervical cancers in general, the increased prevalence of cervical cancers in HIV-infected women has not been documented in South Africa. HIV-infected women with invasive cervical cancer do, however, present approximately 15 years younger at advanced clinical stage than HIV-negative women with invasive cervical cancer.

**GENITAL WARTS**

In line with the greater incidence of HPV infections in HIV-infected women, genital warts are more common. HIV-infected women not on antiretroviral therapy or who have AIDS have the greatest preponderance of this condition. The genital warts are usually extensive, prolific, large, multifocal, involving genitals, anus and buttocks, and are more prone to recurrence. All conventional methods of treatment have been used, but recurrence is overwhelmingly common.

**MENSTRUAL DISORDERS**

HIV-infected women experience higher rates of menstrual irregularities, including amenorrhoea, menorrhagia, intermenstrual bleeding, metrorrhagia and shortened or prolonged cycles. Sporadic reports suggest ovulatory dysfunction and an increased possibility of premature ovarian failure as the cause. The menstrual disorders may not be directly due to HIV infection, but occur for various reasons that are not directly related to the disease. Associated factors, such as wasting, loss of muscle mass,
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In 1993, the CDC included invasive cancer of the cervix as an AIDS-defining illness.

In the HIV-infected woman, contraception must provide fertility regulation, but it must also not increase the risk of transmission or affect the course of the disease. Condoms are probably the mainstay contraceptive and should be encouraged either as the sole contraceptive or in addition to any other form of contraceptive method used. This should also extend to all couples in whom both partners are HIV infected because of the potential risk of transmitting drug-resistant strains of the virus to each other, which may eventually result in treatment failure. Latex condoms are appropriate, although oil-based lubricants, which weaken latex, should be avoided. Until further research provides the necessary data, the female condom, diaphragm and contraceptive sponge should not be used alone for the prevention of HIV transmission, although there is some recent evidence that the female condom may be effective.

Nonoxynol-9, the spermicide, increases the likelihood of genital ulcers and vaginal inflammation and is no longer recommended in HIV-infected women. In fact, recent data indicate that nonoxynol-9 is not effective in preventing gonorrhoea, chlamydia, trichomoniasis, syphilis or HIV infection.

Both the International Planned Parenthood Federation and the World Health Organization have warned against the use of the intrauterine contraceptive device (IUCD) in HIV-infected women due to theoretical concerns about the increased risk of pelvic infection, increased blood loss and female-to-male HIV transmission. More recent data, however, show that there is no change in HIV shedding, no significant difference in overall complication rates or infection-related complications and no association between acquisition of HIV and IUCD usage. The conclusion of some authors is that in developing countries, the IUCD may be a safe contraceptive method for appropriately selected HIV-infected women with continuing access to medical services.

The combined oral contraceptive pill (OCP) is effective in preventing conception but may stimulate recruitment of inflammatory cells to the lower genital tract and cause cervical ectopy, a common side-effect of the OCP. These may play important roles in the acquisition and shedding of HIV. Oestrogens have also been shown to inhibit cell-mediated responses, while progesterone can alter both systemic and mucosal immunity. Competing factors may decrease transmission, however, and these include decreased bleeding and increased cervical mucous viscosity. Data from published studies provide mixed results, with nearly half concluding that OCP increases the risk of HIV transmission, whereas the remainder concluded the opposite. The potential of drug-drug interactions is also a major concern when HIV-infected women use the OCP. A number of antiretroviral drugs activate the cytochrome P450 system and decrease the effectiveness of the OCP, with the risk of contraceptive failure. Rifampicin, used in the treatment of tuberculosis, also decreases the efficacy of the OCP in a similar manner.

Progestational agents may increase the risk of HIV transmission because of their ability to cause atrophy of the vaginal epithelium. Deciding on a contraceptive method is difficult because of the many factors that must be taken into account in the HIV-infected woman, and therefore it is prudent to advocate that, whatever method is chosen, concomitant use of the condom is obligatory.

For many years now the topic of providing assisted reproductive care to couples in whom one or both partners is known to be HIV infected has generated intense controversy. Because life expectancy in HIV-infected adults is increasing due to antiretroviral usage, more are considering becoming parents.

Any option offered to serodiscordant couples has conception as its priority, but at the same time without transmitting HIV to the uninfected partner and/or to the baby.

Options available include:
- **Timed unprotected intercourse** – couples may try to minimise the risk by accurately timing intercourse using ovulation detection methods.
- **Washed intrauterine insemination**, especially for the HIV-infected woman whose partner is not infected.
- **Using polymerase chain reaction (PCR) technology**, cell-associated and free virus can be eliminated from semen, which then is
inserted by intrauterine insemination (IUI). This method is appropriate for the serodiscordant couple in which the man is HIV infected.

- Intracytoplasmic sperm injection – one mature spermatozoon is inserted into an oocyte obtained by ovulation induction. The oocyte is exposed to one spermatozoon only, as opposed to millions when IUI is used. The fertilised ova are then transferred back into the uterus.

- Donor sperm in the case of HIV-infected male and non-infected female.

- Adoption.

Further reading
Sauer MV. American physicians remain slow to embrace the reproductive needs to human immunodeficiency virus-infected patients. Fertil Steril 2006; 85: 295-297.

IN A NUTSHELL

In the age group 15 - 24 years, women are 2.5 times more likely to be HIV infected.

Treatment principles for managing vulvovaginal candidiasis in HIV-positive women should be identical to those used in HIV-negative women.

Approximately 50% of genital ulcers in HIV-infected women will be idiopathic and are called aphthous ulcers, while the rest are most commonly due to herpes simplex virus, mixed bacteria, syphilis, Haemophilus ducrei, mycobacteria or cytomegalovirus infections.

Acyclovir-resistant HSV may be encountered in 11 - 17% of HIV-infected women and valacyclovir, famciclovir, foscarnet or cidovudov may need to be considered.

HIV-positive women with PID have higher temperatures, lower WBC counts, more syphilis, more bacterial vaginosis, less chlamydia, less abdominal tenderness and twice as much tubo-ovarian abscess formation compared with HIV-negative women.

Severe immunosuppression and high viral load significantly increase the likelihood of HPV infections, abnormal smears and SIL, and overall, HIV-infected women have a 5-6-fold increase of developing SIL.

Colposcopic examination is warranted after a single Pap smear shows cytological atypia, ascus, low-grade or high-grade SIL or AGUS in an HIV-positive woman.

Even though ablative or excisional procedures are the treatment of choice for CIN 2 or 3, the need for second or third therapeutic procedures is often required. Hysterectomy is not advocated as there is a 50% rate of recurrence at the vaginal vault.

Menstrual disorders in HIV-infected women may not be directly due to the HIV, but to various factors that are not directly related to the disease.

Condoms are the mainstay of contraception and should be encouraged either as the sole contraceptive or in addition to any other form of contraceptive method used.