Urologic complications of HIV and AIDS

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SUMMARY

In recent years the nature of HIV infection has been dramatically transformed from an invariably fatal disease to a chronic disorder with a relatively benign course. Disease progression from HIV to AIDS and HIV-related mortality can be reduced effectively by several years of treatment with highly active antiretroviral therapy (HAART). For patients who do not have access to HAART, HIV infection continues to be a lethal disorder characterized by opportunistic infection with uncommon organisms (e.g. mycobacteria, fungi, parasites and viruses), as well as lethal malignancies such as Kaposi sarcoma, non-Hodgkin lymphoma and squamous cell carcinoma of the penis or cervix. In patients receiving HAART, urologic complications are likely to be caused by adverse effects of antiretroviral medication (e.g. indinavir urolithiasis) or disorders associated with aging, such as benign prostatic hyperplasia and prostate cancer. Prospective clinical trials have shown that adult male circumcision can reduce the rate of female to male HIV transmission by more than 50%; however, the development of preventive or curative modalities with 100% efficacy remains elusive.

REVIEW CRITERIA
A comprehensive PubMed search of the English-language literature published between January 1980 and March 2008 was made for relevant articles using the Medical Subject Heading terms "HIV", "AIDS" and "urology" or "urological(al)" in various combinations. The reference lists of retrieved articles were assessed for additional articles.

Keywords: AIDS, HIV, urologic complications

INTRODUCTION

HIV is a retrovirus that replicates rapidly and kills helper T cells, which are the body's main cellular defense against infection. HIV is spread through contact with blood, semen and vaginal secretions—for example during homosexual or heterosexual intercourse, by use of contaminated needles or blood products, or from mother to child during birth or through breast feeding.

AIDS refers to the disorder caused by HIV infection. AIDS usually occurs when $CD4^+$ count falls below 200 cells/mm^3. The clinical course of the disease is characterized by recurrent infection by various uncommon opportunistic bacteria, fungi and viruses, which can involve any part of the urogenital system. Despite the aggressive nature of standard therapy, AIDS can have a rapidly fatal course in most patients.

In the past decade, the increasing availability of antiretroviral drugs has helped combat HIV replication and has changed HIV infection from an almost invariably fatal disorder to just another chronic illness. HIV-positive patients who are treated with highly active antiretroviral therapy (HAART) have an almost normal life expectancy, and are now presenting with common urologic disorders that usually affect elderly people. Unfortunately, HAART is not readily available in many of the countries that have the highest prevalence of HIV infection—in these regions AIDS has retained its profile as a severely debilitating and eventually fatal disorder.

Urologic disorders (Box 1) are often the first clinical signs that indicate possible HIV infection. In this Review we discuss the main urologic complications in patients with HIV and AIDS, including complications resulting from treatment.

EPIDEMIOLOGY OF HIV AND AIDS

WHO data show that the global prevalence of HIV infection has leveled off—39.5 million people were affected in 2006 and 33.2 million in 2007. Worldwide, 2.5 million people became newly infected in 2007, and 2.1 million died of AIDS.[1]Although the incidence of new cases has leveled off, the total number of people living with HIV infection is increasing.

Sub-Saharan Africa contains 10% of the world's population but accounts for less than 1% of the world's health expenditure. This region bears more than 70% of the global burden of HIV and AIDS, with an estimated 22.5 million people living with HIV.[2] It is expected that the AIDS death toll in sub-Saharan Africa will continue to rise due to inadequate prevention and reduced treatment efforts compared with other parts of the world; therefore, a substantial increase in the magnitude of the AIDS epidemic is expected during the course of the next 10 years.[3]

In 2007, HIV incidence in Eastern Europe and Central Asia increased by more than 150%. In Vietnam HIV incidence more than doubled between 2000 and 2005, and Indonesia has the fastest growing epidemic.[4] The prevalence of HIV continues to increase in the US, which currently has an estimated 1.2 million people living with HIV; about 74% of cases are in adult men, and the epidemic continues to disproportionately affect African Americans.[5,6]

UROLOGIC COMPLICATIONS OF HIV AND AIDS

RENAL DYSFUNCTION

Acute renal failure in HIV-infected patients is common and is associated with advanced immunodeficiency.[7] Kidney disease and subsequent renal failure is the fourth leading cause of death in HIV-positive patients.[8] Renal dysfunction in patients with HIV can be caused by nephrotoxic medications such as antibiotics and antifungals, metabolic dysfunction and volume depletion as a result of chronic diarrhea, ureteral obstruction from malignancy, infections, and intrinsic diseases such as HIV-associated nephropathy (HIVAN), which occurs in 10–30% of patients with HIV.

One-year mortality in patients with HIVAN is 50%; even in those being treated with HAART it is approximately 30%.[8] HIVAN is characterized by acute decline in kidney function, high-grade proteinuria (more than 3.5 g of protein excreted per day), edema, hypertension and anemia, and is associated with $CD4^+$ counts <350 cells/mm^3. Renal ultrasound usually shows that the kidneys are of normal size but have increased echogenicity. Diagnosis of HIVAN is confirmed with renal biopsy. Histologic findings include focal segmental glomerulosclerosis, usually with tubulointerstitial nephritis.[9]

In a single study from South Africa,[10] renal biopsies in HIV-positive black patients showed that the main histologic categories of kidney disease were classic HIVAN (27%) and HIV-related 'immune complex kidney disease' (21%). Other glomerulonephritides included membranous disease, postinfectious disease, mesangial hyperplasia, and immunoglobulin A nephropathy. Overlapping clinical presentations prevented prebiopsy histologic predictions.[10] Treatment of HIVAN includes HAART, corticosteroids, angiotensin-converting-enzyme inhibitors, and, eventually, renal replacement therapy.[11,12]

Ureteral obstruction can be caused by Burkitt lymphoma that directly involves the ureter[13] or by lymph-node metastases of other malignancies such as Kaposi sarcoma or testis tumors. Patients with ureteral obstruction might require ureteral stenting or percutaneous nephrostomy. The incidence of renal involvement in patients with non-Hodgkin lymphoma who have AIDS is 6–12%, and presentation can be bilateral.[14, 15]

Although patients with HIV are usually excluded from dialysis and renal transplantation, there are now several reports in the literature of successful renal transplantation in HIV-positive recipients on HAART. Gruber and colleagues[16] reported acute rejection rates between 43% and 67% in patients with renal transplants and HIV, and patient and graft survivals of 100% and 88%, respectively.

URINARY TRACT INFECTION

A study in the 1980s reported a 17% incidence of urinary tract infections (UTIs) in HIV-positive patients,[17] but a study in 2003 showed that 38% of patients with HIV had a bacterial infection involving the lungs whereas only 5% of patients had a UTI.[18] There is a greater risk of UTI when the $CD4^+$ count falls below 500 cells/mm^3.[19, 20]

The most common bacterial cause of UTIs in patients with HIV is *Enterococcus faecalis*.[21] Other pathogens that can cause UTIs in patients with HIV are*Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Proteus* spp., *Staphylococcus epidermidis*, group D streptococci, *Serratia* spp. and *Salmonella* spp.[14, 15, 17, 20, 22]Pathogens in the urine of HIV-infected patients have shown high antimicrobial resistance.[23]

Atypical pathogens that have the capacity to cause a UTI in patients with HIV include fungi (*Candida albicans*, *Aspergillus fumigatus*, *Blastomyces* spp.,*Cryptococcus neoformans*, *Cryptosporidium* spp. and *Histoplasma capsulatum*), parasites (*Toxoplasma gondii* and *Pneumocystis carinii*),*Mycobacterium* spp. (*Mycobacterium tuberculosis* and *Mycobacterium avium*complex) and viruses (cytomegalovirus and adenovirus).[24, 25, 26]

In patients with AIDS and reported renal abscesses, satisfactory results have been achieved with only antibiotics and HAART. Percutaneous drainage of renal abscesses and appropriate cultures of aspirated pus are important to diagnose opportunistic infections. Nephrectomy is indicated when conservative therapy fails or septic shock supervenes.[27]

Nosocomial infections are common in patients with HIV because central venous catheters and urinary catheters are often used in this patient population. Bloodstream infections are the most common nosocomial infection, followed by UTIs, vascular infections, and pneumonia. HIV-positive patients are more likely to have nosocomial infections caused by *S. aureus* than by any other pathogen.[28]

BLADDER DYSFUNCTION

Voiding disorders are usually caused by infection (e.g. cystitis or prostatitis), obstruction (e.g. of the bladder neck or urethra) or neurologic disorders (e.g. encephalitis, myelitis or acute idiopathic polyneuritis). Several unusual disorders can also cause neurogenic bladder dysfunction, such as herpetic ascending myelitis, cerebral toxoplasmosis and HIV encephalitis.[29, 30]

Bladder outlet obstruction caused by prostatic enlargement accounts for less than 20% of cases of urinary retention in HIV-positive patients.[29, 30, 31] As HIV survival and the mean age of patients on HAART increases, however, there will be an increased incidence of symptoms and complications due to benign prostatic hyperplasia.

Patients with AIDS are also at risk of developing non-Hodgkin lymphoma or rare infections of the bladder by *T. gondii*; cystoscopic bladder biopsies are needed to make the diagnosis.[32]

TUBERCULOSIS

The incidence of tuberculosis has tripled during the past two decades in countries with a high prevalence of HIV.[33] About a third of people living with HIV worldwide are infected with tuberculosis. Patients who are HIV positive and are not infected with tuberculosis have a 10–15% risk of developing the infection.[33] Tuberculosis has become the leading cause of death among HIV-positive patients in Africa and is the most common presenting illness among people with HIV who are taking HAART.[34] In many developing countries, concurrent HIV and tuberculosis epidemics have considerably affected already poor public health services.

Active tuberculosis might be associated with a high HIV viral load, low $CD4^+$counts and rapid progression of HIV infection to AIDS.[35] In patients who are immunocompromised, tuberculosis will usually manifest as a severe systemic infection with bacteremia, disseminated lesions and multiple parenchymatous renal foci.[36]

Patients with AIDS who have urogenital tuberculosis (UGTB) tend to be younger than HIV-negative patients with UGTB (median age 26 years vs 35 years). Patients with AIDS and UGTB usually have fever, a high probability of parenchymatous renal involvement and disseminated tuberculosis, a low prevalence of storage symptoms and stenosis of the collecting system, and contracted bladder (Figure 1). In addition, the disease course is usually shorter in patients with AIDS who have UGTB than in patients with only UGTB. In patients with AIDS, UGTB often has systemic symptoms, multiple parenchymatous renal foci, and a low frequency of lesions of the collecting system, and can develop into disseminated TB.[33]

Drug treatment is the first-line strategy in patients with UGTB. Treatment regimens of 6 months are effective in most patients.[36] Patients with HIV and tuberculosis being treated with HAART should be carefully observed with respect to sequencing of treatment, the value of directly observed therapy, and the possibility of pharmacokinetic drug interactions that could result in toxicities, particularly hepatotoxicity and neuropathy.[37, 38]

Despite effective drug therapy, surgery in the form of ablation (e.g. nephrectomy) or reconstruction (e.g. augmentation enterocystoplasty) might be unavoidable. Both radical and reconstructive surgery should be carried out after at least 2 months of intensive anti-TB drug therapy.[33]

PROSTATITIS AND PROSTATIC ABSCESS

The estimated incidence of acute bacterial prostatitis increases from 1% to 2% in the general population to 3% in asymptomatic HIV-positive patients and 14% in patients with AIDS.[39] The incidence of prostatic abscesses in patients with AIDS, however, has substantially decreased with the advent of HAART; abscesses usually only occur in patients with very low $CD4^+$ counts.[14]

Urine culture is usually negative in men with prostatitis and AIDS, but cultures from the prostate can show unusual organisms such as *S. aureus*,*Enterococcus* spp., *M. tuberculosis*, *M. avium*, *Cryptococcus* spp., *H. capsulatum*, *C. albicans*, or cytomegalovirus.[40, 41, 42]

CT and transrectal ultrasound of the prostate are both accurate methods of diagnosing prostatic disorders in patients with HIV; transrectal ultrasound is perhaps the more useful modality if aspiration or biopsy is required.[20] A prostatic abscess can be managed with aspiration, drainage through the perineal route, or transurethral unroofing. Antibiotic therapy should initially include parenteral bactericidal agents such as broad-spectrum penicillin derivatives, third-generation cephalosporins with or without aminoglycosides, or fluoroquinolones.[14, 20] Long-term antibiotic therapy is essential to avoid recurrent infection.[43]

EPIDIDYMO-ORCHITIS AND FOURNIER GANGRENE

In sub-Saharan Africa, tuberculous epididymitis is often reported in patients with AIDS. Fungal infection with *H. capsulatum*, as well as cytomegalovirus, can involve the testis and epididymis (or both testes and epididymes) in HIV-positive men.[44]

Fournier gangrene (necrotizing fasciitis of the external genitalia) can be the first clinical presentation in patients with HIV infection.[6, 45, 46] Immediate diagnosis with wide surgical debridement of necrotic and nonviable tissue is necessary.[47] Broad-spectrum antibiotic therapy for aerobic Gram-positive and Gram-negative bacteria, as well as for anaerobic microorganisms, is necessary while awaiting the results from culture and sensitivity tests.[48] Hyperbaric oxygen can be useful in the treatment of Fournier gangrene.[49]

PARASITIC INFESTATIONS

Regions with a high prevalence of helminthic parasite infestations also have a high prevalence of HIV and AIDS.[50] Interaction of the pathogen with host $CD4^+$T cells is a characteristic of HIV infection as well as parasitic infestations, and parasitic infection can alter the disease course of tropical diseases such as schistosomiasis and malaria. On the other hand, tropical infections can ease transmission of HIV and accelerate progression from asymptomatic HIV infection to AIDS.[51]

In rural Africa, women with genital schistosomiasis have a three-fold higher risk of having HIV than women who do not have schistosomiasis.[52] In addition, HIV-positive women are more likely to have malaria or lymphatic filariasis than are HIV-negative women. Mother to child transmission of HIV is substantially more likely in women coinfected with one or more helminthic parasite than in those with no helminthic infection; transmission possibly takes place via a mechanism in which parasite antigens activate lymphocytes *in utero*.[53]

HIV infection can hinder the diagnosis of parasitic infestations, or reduce the efficacy of antiparasitic treatment.[51] In a study by Mwanakasale and co-workers,[54] HIV-positive patients with schistosomiasis excreted fewer parasite eggs and had fewer symptoms of hematuria than HIV-negative patients; the sensitivity and positive predictive value of hematuria as an indication of substantial infection was lower in the group of patients coinfected with HIV.

MALIGNANCIES ASSOCIATED WITH HIV AND AIDS

AIDS-associated malignancies (AAMs) include Kaposi sarcoma, non-Hodgkin lymphoma and invasive cervical cancer. In the past decade there has been a significant reduction in the incidence of Kaposi sarcoma and non-Hodgkin lymphoma in patients with AIDS, probably as a result of HAART; the incidence of cervical carcinoma, however, has not decreased.[55, 56, 57] On the other hand, HIV-positive patients still have a higher risk of developing Kaposi sarcoma and non-Hodgkin lymphoma than the general population.[58] From 1992 to 2002, the most common malignancies in the HIV-positive population were Kaposi sarcoma, lymphoma (Hodgkin and non-Hodgkin), cervical cancer, liver cancer, testicular cancer, and melanoma.[59]

In patients with HIV on HAART there has been an increase in the incidence of non-AAMs, including anal cancer, lung cancer, hepatocarcinoma, vaginal cancer, leukemia, oropharyngeal cancer, colorectal cancer, penile cancer, and renal cancer.[55, 56, 57, 59, 60]

Non-AAMs—such as lung, skin, penile, laryngeal, tongue and colorectal cancer—are likely to occur at a younger age in HIV-positive patients than in HIV-negative individuals (47.6 years vs 60.3 years); HIV-positive patients also seem to have a lower clinical stage of disease with these cancer types. Patients with HIV and a non-AAM are usually quite young at diagnosis; this fact might be partly associated with early detection and pre-existing immunosuppression.[61]

Possible explanations for the high prevalence of non-AAMs might include the following factors: longer survival of patients on HAART, with only partial immune recovery achieved in most patients; high incidence of human papillomavirus (HPV), Epstein–Barr virus, and hepatitis C virus coinfection in patients with HIV infection; and potential oncogenicity of long-term HIV infection or long-term HAART.[62] Other proposed mechanisms of carcinogenesis include decreased immune surveillance, a direct effect of viral proteins, cytokine dysregulation, or other immunologic or viral cofactors.[63]

The outcome for HIV-infected patients with cancer has substantially improved in the HAART era, probably due to the fact that the treatment considerably improves the immune status and bone marrow function. Current studies suggest that patients with AAMs can be treated with conventional modalities such as chemotherapy and radiotherapy and with appropriate use of supportive measures.[64]

KAPOSI SARCOMA

Kaposi sarcoma is often a presenting sign of HIV and AIDS.[65] Before the advent of HAART, up to 20% of patients infected with HIV were affected by Kaposi sarcoma. This percentage has decreased by approximately 90% since the introduction of HAART.[66] The cause of this rare cancer is human herpes virus type 8.[66] Kaposi sarcoma is more common in men and usually comprises a systemic disease that affects internal organs, including the kidneys and testes.[67] About 20% of HIV-positive men with Kaposi sarcoma have genital involvement, which can lead to complications such as lymphatic or urethral obstruction or (rarely) penile necrosis and gangrene as a result of vasculitis or vascular obstruction (Figure 2).[68]

The first step in treatment for Kaposi sarcoma in patients with HIV is to initiate HAART or to optimize the HAART regimen, which generally results in remission of Kaposi sarcoma.[69] Local therapy for cosmetically disturbing or painful lesions can include the following treatment options: laser therapy; cryotherapy; surgical excision; application of topical retinoids (e.g. 9-cis-retinoic acid and alitretinoin); use of intralesional bleomycin, interferons or vinca alkaloids; X-ray radiation; electron beam therapy; or cobalt radiation.[66] Disseminated or visceral Kaposi sarcoma is treated with combination chemotherapy. The gold standard combination therapy of adriamycin, bleomycin and vincristine has been replaced in recent years with liposomal anthracyclines, such as daunorubicin and doxorubicin.[69, 70] Paclitaxel is also effective in treating advanced Kaposi sarcoma.[71] Suprapubic cystostomy might be necessary until definitive treatment takes place.[72] Despite widespread availability of HAART and chemotherapy, Kaposi sarcoma continues to be a substantial clinical problem in patients with HIV, with only 50% of individuals achieving complete resolution of disease.[73]

TESTICULAR TUMORS

Early studies have suggested that the incidence of testicular tumors in immunocompromised patients is between 20 times and 57 times that of the general population, and that germ cell testicular tumors are the third most common AIDS-associated malignancy.[74] Despite the high prevalence of HIV infection in sub-Saharan Africa, there have been no reports of a significant increase in germ cell testicular tumors in this region. A more recent study indicated that the relative risk for testicular seminoma in HIV-positive patients compared with HIV-negative individuals is around 2.[75] Non-Hodgkin lymphoma of the testes can present bilaterally and is usually disseminated at the time of presentation.[76] Once considered to be poor candidates for radiation and chemotherapy, HIV-positive patients with non-Hodgkin lymphoma of the testes are currently thought to have equal morbidity and response to patients who do not have HIV.[77] Complete remission is reported in 50–75% of patients with systemic treatment;[78] however, the incidence of relapse and rapid progression might be higher in immunocompromised men than in the general population.[14,15]

PENILE CANCER

Individuals infected with specific HPV subtypes are at risk of developing squamous cell carcinomas after a long period of latency (Figure 3).[79] About 40–45% of patients with penile carcinoma have evidence of HPV DNA;[80] however, factors other than HPV can also play a part in the pathogenesis of penile cancer.[81]

Certain types of HPV are associated with squamous cell carcinoma (Figure 3). In a study of HIV-infected men, a high prevalence of high-risk HPV types (16 and 18) was found in the anus, penis and mouth (78%, 36% and 30%, respectively), without evidence of pathology in these areas.[82] The relative risk of penile cancer in HIV-positive patients is four times higher than that in HIV-negative men.[75]

HIV-infected homosexual men have a substantially increased risk of HPV-induced anal cancer and anal intraepithelial neoplasia, and a moderately increased risk of penile cancer.[83] In a study by Kreuter and colleagues[84] of HIV-positive men, penile intraepithelial neoplasia was detected in 4.2% and anal intraepithelial neoplasia was found in 59% of these patients. Urethral and bladder involvement with condylomata acuminata caused by HPV is usually associated with immunosuppression.[85]

Squamous cell carcinoma of the penis is usually more aggressive in HIV-positive patients than in individuals without HIV and should be excised and staged. Regional lymphadenectomy, radiation, or systemic chemotherapy should be used, in a similar approach to treatment for individuals not infected with HIV.[86]

PROSTATE CANCER

It is not clear whether there is a decreased incidence of prostate and breast cancer in HIV-positive patients.[55, 56, 57, 59] With the increased life expectancy of HIV-positive men on HAART, however, prostate cancer in this population is expected to become an increasingly more important health problem.

Despite a case report suggesting that prostate cancer in HIV-positive men might be unusually aggressive,[87] prostate cancer has a similar disease course in men with HIV as that in HIV-negative men. With improved therapies for HIV and increasing survival, the importance of screening for and treating prostate cancer is increasing.[88]

It has been recommended that the standard PSA assessment should be done in HIV-positive patients, without the need for adjustments.[89] Some clinicians advocate PSA screening of HIV-positive patients in their early forties because of the potential for prostate cancer to present in a disseminated manner with nonspecific features.[87, 90]

HIV-positive patients who have asymptomatic prostate cancer should be offered all possible treatment options, including surgery, radiation, androgen deprivation, and observation. Some clinicians believe that laparoscopic or robot-assisted surgery should be performed when possible to minimize the risk of postsurgery complications.[91] In a meta-analysis of 12 publications providing detailed information on 60 patients with HIV and prostate cancer, early outcomes of treatment did not demonstrate increased acute morbidity; however, long-term outcomes have not been reported.[88]

SEXUAL DYSFUNCTION AND INFERTILITY IN PATIENTS WITH HIV AND AIDS

ERECTILE DYSFUNCTION

Testicular atrophy is common in men with AIDS and can predispose patients to infertility, erectile dysfunction (ED) and reduced libido. Studies both support and oppose the occurrence of sexual dysfunction in HIV-positive men taking HAART.[92, 93, 94, 95] Men who are HIV positive are more likely to have symptoms of depression than are men without HIV.[96, 97] This correlation might be associated with low libido and ED; however, common antidepressant medications such as selective serotonin reuptake inhibitors can also decrease libido and sexual performance.[98] Phosphodiesterase-5 inhibitors might allow patients to recommence sexual activity and regain confidence, which can improve depressive symptoms.[99] The use of testosterone in muscle-wasting disorders such as HIV has also been suggested as a treatment option.[100]

Effective treatment of ED can increase the risk of spreading HIV.[101] Benotsch*et al*.[102] have shown that men who took phosphodiesterase-5 inhibitors had higher rates of sexually risky behavior. This observation means that there might be an ethical dilemma in treating ED in HIV-positive patients.[103] It is important to improve patients' quality of life, but equally important to help stop the spread of the virus; therefore, detailed counseling of HIV-positive men with ED is essential.[104]

INFERTILITY

Abnormal semen parameters can be associated with atrophy of the testes. Atrophy might be the result of hypothalamopituitary axis dysfunction, inflammation, infection, chronicity of disease, malnutrition, or a direct cytotoxic effect of HIV on germinal tissue.[77]

If an infertile couple with one HIV-positive partner wants to have a child, the risk of HIV transmission has to be considered. HIV transmission rates for unprotected heterosexual intercourse are 1 case per 1,000 contacts (male to female transmission) to less than 1 case per 1,000 contacts (female to male transmission).[105] Sperm washing for couples where the man is infected with HIV, followed by assisted reproduction techniques, has proved to be the safest method for infertility treatment in HIV-positive couples.[106, 107] Tested sperm carry a 10% risk of harboring the virus, so patients and offspring are still at risk; however, more than 500 children have been born after sperm washing, with no instances of seroconversion.[105]

UROLOGIC COMPLICATIONS AFTER ANTIRETROVIRAL TREATMENT

UROLITHIASIS

Indinavir is an antiretroviral drug that works as a protease inhibitor and prevents the formation of new viral particles. About 20% of indinavir is not metabolized and is excreted in the urine.[108, 109, 110, 111] The drug can cause intrarenal crystal deposition, which can lead to acute renal failure.[112] A total of 80% of patients with urologic complications have raised indinavir plasma concentrations, indicating that plasma levels should be carefully monitored and the indinavir dosage reduced if necessary.[113, 114]

Indinavir causes urolithiasis in 5–25% of HIV-positive patients treated with the drug.[115, 116] Contributing causes of urolithiasis include diarrhea leading to dehydration, increased urinary concentration, acidification, and hypocitraturia.[115, 117] Indinavir is reported as a stone component in only 29% of calculi. The remaining stone components are calcium oxalate, ammonium acid urate, and uric acid.[115, 117]

Urolithiasis can in turn cause acute renal colic or severe azotemia. Pure indinavir stones are radiolucent and might escape detection by plain X-ray and CT (Figure 4).[112, 115, 118, 119, 120] Treatment

consists of interrupting indinavir administration temporarily, giving narcotic analgesics, increasing oral fluid intake (until urine production reaches 2 l/day or more) and acidifying the urine by oral administration of the amino acid L-methionine.[111, 118, 119] Double-J ureteral stents can be inserted if the patient experiences persistent fever or intractable pain.[112] Since indinavir stones are usually gelatinous in consistency, extracorporeal shock wave lithotripsy will not be effective.[112, 120]

RENAL DYSFUNCTION

HAART regimens have a relatively low but clinically significant nephrotoxic potential.[121] Acute tubular toxicity, crystal nephropathy, and acute interstitial nephritis are among the common renal manifestations of HAART nephrotoxicity. Adefovir and tenofovir are associated with tubular toxicity. Indinavir is associated with crystalluria, crystal nephropathy and nephrolithiasis. Acute interstitial nephritis has been reported in patients taking indinavir and atazanavir. Rarely, enfuvirtide can promote glomerulopathy. Frequent exposure to other nephrotoxic non-antiretroviral drugs (e.g. antibiotics, antifungals) also contributes to kidney disease.[122]

HIV PREVENTION AND MALE CIRCUMCISION

The mainstay of HIV prevention is the so-called ABC approach (abstinence, 'be faithful', condom use). Mother to child transmission can be minimized if cesarean section is performed along with intrapartum infusion of antiviral medications.[15]

The hypothesis that uncircumcised men are at greater risk of acquiring HIV or other sexually transmitted infections than men who have been circumcised is based on several plausible biological mechanisms. These mechanisms include susceptibility of the mucosal surface of the prepuce to trauma, longer survival of pathogens in warm and moist subpreputial spaces, and lack of keratinization and high density of HIV target cells in the inner foreskin compared with the keratinized surface of the outer foreskin and glans.[123, 124, 125, 126, 127]

Epidemiological studies in areas with a low prevalence of male circumcision and a high prevalence of HIV support this hypothesis.[128, 129] A meta-analysis of studies that adjusted for potential confounders reported a large and highly significant reduced risk of HIV infection in circumcised men (adjusted risk ratio 0.42).[123, 130]

Three prospective, randomized clinical trials of adult male circumcision in South Africa, Kenya, and Uganda have reported highly significant reductions in risk of HIV infection among participants randomly assigned to circumcision.[131, 132, 133] The overall risk ratio compared with no circumcision was 0.42 (95% CI 0.31–0.57), which corresponds with a 58% increase in protection (95% CI 43–69%).[134] Apart from absolute sexual abstinence and rigorous condom use, there is currently no preventive measure that has been shown to be more effective than adult male circumcision.

CONCLUSIONS

Since the advent of HAART, the prognosis of HIV-infected patients has improved dramatically and the life expectancy for patients with access to HAART currently seems to be similar to that of HIV-negative individuals. Urologic complications in HIV-infected patients who receive HAART are mostly resultant adverse effects of treatment, in particular renal dysfunction, which is in many cases due to antiviral, antibacterial or antifungal medication, and urolithiasis, caused by the antiretroviral drug indinavir. In patients who do not have access to HAART the prognosis of HIV remains dismal, with eventual progression to AIDS and death being virtually inevitable. Urologic complications in patients with HIV are often the result of opportunistic infections by mycobacteria, parasites, fungi and viruses, or comprise unusual malignancies such as Kaposi sarcoma and non-Hodgkin lymphoma. Prospective clinical trials have conclusively shown that adult male circumcision reduces the risk of female to male

HIV transmission by more than 50%, which is a higher success rate than any other preventive measure except complete sexual abstinence, absolute monogamy or rigorous condom use. Further research is needed to develop preventive or curative modalities with significantly greater efficacy and fewer adverse effects than the currently available options.

KEY POINTS

- Several regions worldwide still do not have access to highly active antiretroviral therapy (HAART); patients with HIV who do not receive HAART are at a high risk of developing opportunistic infections, which usually originate in urologic organs
- Urologic complications are often the first clinical signs of HIV and AIDS
- In patients with HIV and AIDS, urologic complications are typically the result of infection by mycobacteria, parasites, fungi and viruses
- Urologic complications of HIV and AIDS include renal dysfunction, urinary tract infection, bladder dysfunction, urogenital tuberculosis, prostatitis, prostatic abscess, epididymo-orchitis, Fournier gangrene, urologic malignancies, sexual dysfunction and infertility
- There is some evidence that adverse effects of HAART cause urologic complications such as urolithiasis and renal dysfunction
- Prospective clinical trials have shown that adult male circumcision reduces the risk of female to male HIV transmission by more than 50%; however, further research is still needed

BOX 1 UROLOGIC COMPLICATIONS OF HIV AND AIDS.

Kidneys

- Renal dysfunction and/or renal failure
- HIV-associated nephropathy
- Nephrotoxicity from medication (e.g. from HAART)
- Renal abscess
- Renal tuberculosis
- Urolithiasis (especially indinavir stones)

Ureters

- Obstruction by tuberculosis or malignancy (e.g. lymphoma)

Bladder

- Urinary tract infection by Gram-negative or Gram-positive bacteria, or by atypical pathogens (e.g. mycobacteria, fungi, parasites and viruses)
- Voiding dysfunction (caused by neurological disorders or bladder outlet obstruction)

Prostate

- Prostatitis and prostate abscess
- Prostate cancer

Scrotum and testes

- Epididymo-orchitis
- Fournier gangrene
- Kaposi sarcoma
- Germ cell testis tumor
- Non-Hodgkin lymphoma
- Hypogonadism
- Erectile dysfunction
- Infertility

Penis

- Condylomata acuminata (caused by human papillomavirus infection)
- Squamous cell carcinoma

Abbreviation: HAART, highly active antiretroviral therapy.

Figures

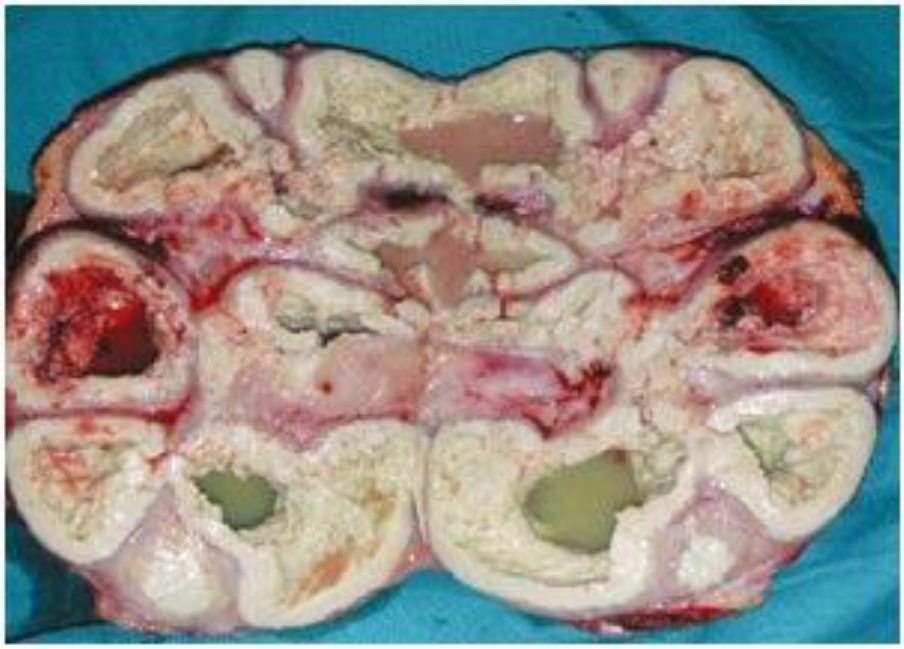

Figure 1 Tuberculous pyonephrosis with widespread caseous necrosis of the renal parenchyma in an HIV-positive patient with a low $CD4^+$ cell count

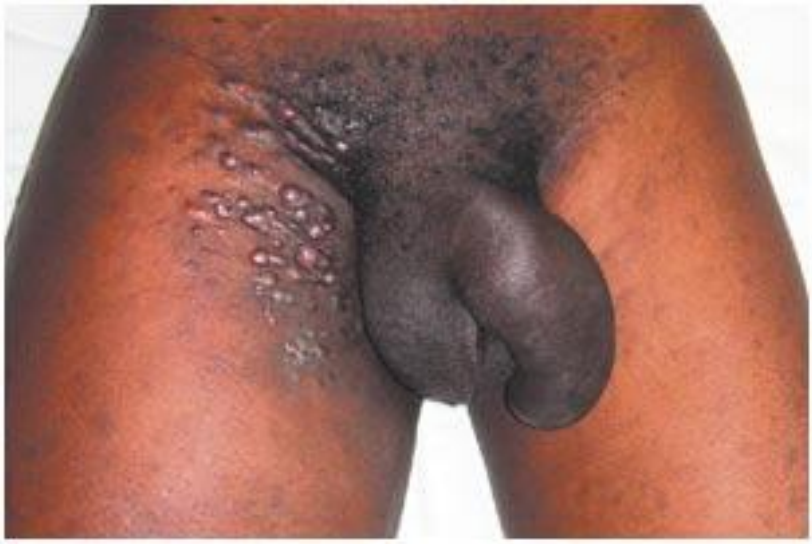

Figure 2 Kaposi sarcoma causing lymphedema of the penis, scrotum and right leg due to inguino-pelvic lymph-node metastases in an HIV-positive man

Figure 3 Extensive squamous cell carcinoma of the penis involving the scrotum and inguinal lymph nodes in an HIV-positive patient with a low $CD4^+$ cell count

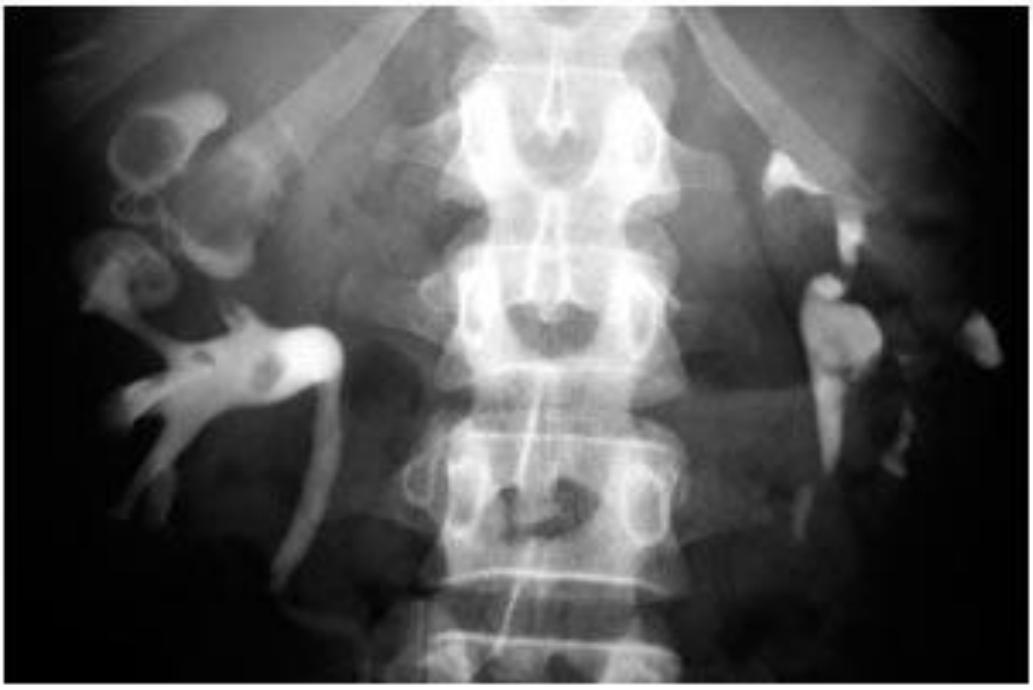

Figure 4 Excretory urogram (intravenous pyelogram) shows filling defects in the renal collecting system due to urolithiasis in a patient with AIDS receiving treatment with indinavir

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