

HIV / AIDS – implications for the urologist

“It’s no fun to have HIV even though it’s viewed as a chronic, controllable disease. It means being wedded to the health system.”

- Philip Berger, Associate Professor in the Department of Family and Community Medicine, Toronto, Canada; and leading advocate on finding health solutions for people living with HIV / AIDS.

BY RICHARD CETTI AND JOHN LAZARUS

Introduction

The human immunodeficiency virus (HIV) is a lentivirus that causes the acquired immunodeficiency syndrome (AIDS), a condition in humans in which progressive failure of the immune system results in life-threatening opportunistic infections and cancers. Without treatment, average survival time after infection with HIV is estimated to be 9 to 11 years. AIDS itself was first described in 1981, and HIV subsequently identified in 1986. By 2012 an estimated 35 million people were living with HIV worldwide, although the incidence of new cases is decreasing [1]. In the UK they have continued to decline from a peak at 7892 in 2005 to 6000 in 2013 [2]. Where previously the focus of urological complications in HIV patients was atypical infections, tuberculous disease and retroperitoneal malignancy; the introduction of highly effective anti-retroviral therapies has shifted the management paradigm from AIDS defining illnesses to those of chronic diseases of ageing.

Infectious complications

- **Genital infections:** These are characterised by viral and sexually transmitted infections. Human papilloma virus (HPV) 6/11/16/18 associated condylomata and (HSV) 2 herpes vegetans can mimic penile cancer. Treatment is local fulguration or topical fluorouracil in the case of HPV, or acyclovir / famciclovir / diofiovir +/- imiquimod in HSV. Rarely condylomata of HPV can

occur in the urethra and bladder, requiring resection. Florid disease has been successfully treated with chemo-radiotherapy. Genital ulcers are usually caused by sexually transmitted diseases (STD) such as genital herpes and syphilis. Occasionally they can occur as part of a systemic illness secondary to cytomegalovirus (CMV) or herpes zoster. Co-infection with syphilis increases the HIV blood viral load and decreases the CD4 count. Genital ulcer disease also increases the risk of HIV transmission. Diagnosis is made by viral swabs of the ulcer bed and blood serology. Cellulitis of the perineum and Fournier’s gangrene also occur more commonly in HIV patients.

- **Urinary tract:** Urinary tract infection (UTI) is common in HIV patients. The likely culprit remains *E.coli*, and work-up for these patients should be similar for other simple and complicated infections in immunocompetent individuals. However, unusual bacteria and atypical infections can occur. *Pseudomonas aeruginosa* is seen in up to a third of HIV patients with UTI [3]. More unusual fungal, viral, mycobacterial and parasitic infections are outlined in Table 1, and highlight the need to ensure cultures are obtained prior to commencing any anti-microbial treatment. Broad spectrum antibiotics should be avoided. In autopsy studies renal tuberculosis (TB) was identified in 6-23% of patients with AIDS. Twenty

percent had subclinical disease. TB diagnosis requires serial early-morning urine cultures (at least three) for acid-fast bacilli (AFB), with a sensitivity of 65% and a specificity of 100%, but can take up to six weeks. More rapid diagnosis can be achieved with PCR assays if available. TB is associated with renal and psoas abscesses. Emphysematous pyelonephritis is seen in HIV patients, however, without the common associations with diabetes mellitus, obstruction and urolithiasis. Prostatitis is more common in men with AIDS affecting up to 14% [3].

- **Immune reconstitution inflammatory syndrome (IRIS):** Immune reconstitution inflammatory syndrome (IRIS) occurs in 11-23% patients with HIV / AIDS, usually within a few weeks of commencing antiretroviral therapy (ART) [4]. As CD4 counts rise sub-clinical infections may be unmasked, or a recovering immune system may respond to a previously acquired opportunistic infection with an overwhelming inflammatory response that paradoxically makes the symptoms of infection or malignancy worse. From a urological viewpoint relevant culprits are: TB; genital herpes and candidiasis; Kaposi’s sarcoma and retroperitoneal non-Hodgkin’s lymphoma (NHL).

Renal dysfunction and transplant

Acute and chronic renal dysfunction is more common in men with HIV. This

Table 1: Opportunistic urological infections in HIV / AIDS.

Fungal

- Candida albicans
- Aspergillus
- Blastomyces
- Cryptosporidia
- Cryptococcus neoformans

Mycobacterium

- M Tuberculosis
- M avium complex

Parasitic

- Toxoplasma gondii
- Pneumocystis carinii

Viral

- Cytomegalovirus (CMV)

Table 2: Nephrotoxic medications used in HIV patients.

ART

- Indinavir
- Ritonavir

Anti-virals

- Acyclovir
- Cidofovir

Antibiotics

- Aminoglycosides
- Rifampacin

Anti-fungals

- Amphotericin

may occur due to intrinsic renal issues, nephrotoxic medication (Table 2), or post renal obstruction secondary to retroperitoneal malignancy or stone disease. HIV associated nephropathy (HIVAN) typically occurs in patients with low CD4 counts and high blood plasma viral loads (BVL). The condition is characterised by severe proteinuria (>3.5g/day) and a histological diagnosis of focal segmental glomerulosclerosis. Treatment consists of ART, angiotensin-converting-enzyme (ACE) inhibitors, steroids and dialysis. The one-year mortality is as high as 30% [5].

As life expectancy on ART has increased so has the risk and incidence of chronic kidney disease (CKD). HIV infection should not preclude a patient from being considered for renal transplant. From 2005 UK national guidelines support kidney transplant in HIV positive patients if CD4 counts are >200cells/mm³ and have undetectable viral ribonucleic acid (RNA) levels for

up to six months prior to surgery. A recent UK series demonstrated an elevated risk of acute graft rejection, but acceptable short-term outcomes with overall survival of 91.3% at three years [6].

Stone disease

The prevalence of stone disease in the general population is increasing in part due to a rise in obesity, and diets high in salt and purines. This is reflected in patients with HIV / AIDS who are also at increased risk from the specific use of protease inhibitors and general factors such as malnutrition, dehydration, hypocitraturia and urinary acidification. The protease inhibitors (PI) indinavir, lopinavir, atazanavir, darunavir, amprinavir and nelfinavir are all cleared renally and can potentially form crystals and stones. It is estimated that 5-25% of patients on indinavir treatment have stone disease [7]. Recent studies have shown that the incidence of stones is even higher on atazanavir, which is of clinical significance as it is now being widely prescribed in first-line ART due to its advantages of once-daily dosing, high virological efficacy and lower rates of gastrointestinal disturbance than other PI's [8]. PI stones provide a diagnostic challenge as they are radiolucent on plain radiography and CT. If there is clinical suspicion supported by findings of hydronephrosis, perinephric stranding, and / or filling defects on contrast studies, the patient should be managed with primary ureteroscopy.

Andrological complications

There is a relatively high incidence of erectile dysfunction in HIV positive men on ART. It remains controversial whether the ART itself is the cause or a result of multiple factors including psychosocial issues. Management of these patients should follow the same principles as with the general population. Clearly an ethical issue arises in whether men re-acquiring erections will pursue high-risk behaviour. Studies have suggested that is not the case, and that good erections facilitate effective condom use [9]. ART drugs such as ritonavir and saquinavir block activity of the CYP3A enzyme leading to a 3-10 fold increase in the serum concentrations of the PDE5i sildenafil; thus dosages should be reduced in men on these particular ART's [10].

Infertility may occur secondary to testicular atrophy. This may

“The introduction of highly effective anti-retroviral therapies has shifted the management paradigm from AIDS defining illnesses to those of chronic diseases of ageing.”

be in part due to disruption of the hypothalamo-pituitary axis, HIV infection itself, secondary infection or pharmacotoxicity. Semen analysis characteristically shows oligoteratospermia. Approximately 5% of men on ART with an undetectable viral load have detectable HIV in their semen. HIV is present in the ejaculate as a free virus but also in the acrosomal head of spermatozoa. Assisted conception (sperm washings, intracytoplasmic sperm injection) in sero-discordant couples may reduce the risk of transmission.

Malignancy

Malignancy is more common in HIV affected persons than age-matched immunocompetent individuals due in part to decreased immune surveillance and the direct action of opportunistic viral infection and proteins. Since the introduction of ART, AIDS defining cancers (ADC) have relatively decreased in incidence (apart from cervical and anal cancer), being replaced by non-ADC, now comprising 70% of diagnoses [11].

- Kaposi's sarcoma (KS) is a tumour caused by infection with human herpes virus 8 (HHV8). It is a systemic disease and can affect any organ, although the kidney rarely. It affects up to a quarter of HIV patients not on ART, with genital lesions occurring in up to 20%.
- Non-Hodgkin's lymphoma (NHL) is usually aggressive and disseminated at time of diagnosis. It may involve the testicles bilaterally, kidneys and retroperitoneum leading to obstructive renal failure requiring stents or nephrostomies. Orchidectomy and chemo-radiotherapy are treatment options,

although overall three-year survival rates are only approximately 50%.

- Cervical cancer in HIV-positive women is often more advanced at presentation. This increases the risk of fistula disease, ureteric obstruction and renal failure. Stenting, nephrostomy or palliative diversion may be required.
- Prostate cancer is likely to be an increasing issue in men with HIV as life expectancy increases with ART. Studies have shown that prostate specific antigen (PSA) levels rise with age but do not differ with HIV status, and that median age of diagnosis is the same as the general population [12]. Discussion about screening, and subsequent treatment, should be undertaken in line with that of the general population.
- Renal cancer: The incidence, clinical presentation and prognosis of renal cancer are all similar between HIV affected individuals and the general population. Management should also be similar.
- Bladder cancer: May occur more commonly in HIV positive patients, although the literature is contradictory. It does appear that it may present at an earlier age, and be relatively advanced at diagnosis with a higher proportion of non-transitional cell carcinoma and transitional cell carcinoma (TCC) with squamous differentiation, with a higher risk of local relapse and metastasis [13].
- Testis cancer: Early data suggested an association with an increased risk of seminoma in those with AIDS, secondary either to decreased immune surveillance, or HIV associated testicular atrophy. Contemporary data in the ART era suggests that this risk no longer applies [14].
- Penile cancer: Carcinoma in situ (CIS) and verrucous cancer associated with HPV infection occur more commonly in HIV patients. The diagnosis and management of these men is the same as the general population.

Fistulae

Entero-vesical fistulae may be a result of bladder involvement by KS, NHL, TB or cryptosporidiosis, and should be excluded in any patient with recurrent UTI or pneumaturia.

Circumcision and HIV

Three large randomised prospective clinical trials have demonstrated a 50-60% reduction in the risk of HIV infection following circumcision [15]. This is demonstrable only in transmission from woman to man and not vice versa, with outcomes between homosexual men unclear. The mechanism behind this is threefold: in reducing the number of HIV target cells, improving the keratinisation and hence protection of the glans from abrasions, and reducing the risk of local balanoposthitis which recruits Langerhans cells, another target of the HIV virus. Circumcision undertaken for this indication must be accompanied by adequate counselling to avoid subsequent high risk behaviour.

References

1. UNAIDS. Report on the global AIDS epidemic. 2013. http://www.unaids.org/sites/default/files/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf Last accessed March 2015.
2. Public Health England. National HIV surveillance data tables. 2014. www.gov.uk/government/statistics/hiv-data-tables Last accessed March 2015.
3. Hyun G, Lowe FC. AIDS and the urologist. *Urol Clin North Am* 2003;**30**(1):101-9.
4. Meintjes G, Scriven J, Marais S. Management of the immune reconstitution inflammatory syndrome. *Curr HIV/AIDS Rep* 2012;**9**(3):238-50.
5. Atta MG. Diagnosis and natural history of HIV-associated nephropathy. *Adv Chronic Kidney Dis* 2010;**17**(1):52-8.
6. Gathogo EN, Hamzah L, et al. Kidney transplantation in HIV-positive adults: the UK experience. *Int J STD AIDS* 2014;**25**(1):57-66.
7. Masarani M, Dinneen M, Coyne KM, Hawkins DA. The genitourinary complications of HIV infection in men. *Br J Hosp Med (Lond)* 2008;**69**(3):141-6.
8. Arumainayagam N, Gresty H, Shamsuddin A, et al. HIV related stone disease- a potential new paradigm? *BJU Int* 2014; [Epub ahead of print].
9. Sanders SA, Milhausen RR, Crosby RA, et al. Do phosphodiesterase type 5 inhibitors protect against condom-associated erection loss and condom slippage? *J Sex Med* 2009;**6**(5):1451-6.
10. Heyns CF, Smit SG, van der Merwe A, Zarrabi AD. Urological aspects of HIV and AIDS. *Nat Rev Urol* 2013;**10**(12):713-22.
11. Crum-Cianflone N, Hullsiek KH, Marconi V, et al. Trends in the incidence of cancers among HIV-infected persons and the impact of antiretroviral therapy: a 20-year cohort study. *AIDS* 2009;**23**(1):41-50.
12. Shiels MS, Pfeiffer RM, Engels EA. Age at cancer diagnosis among persons with AIDS in the United States. *Ann Intern Med* 2010;**153**(7):452-60.
13. Chawki S, Ploussard G, Montlahuc C. Bladder cancer in HIV-infected adults: an emerging concern? *J Int AIDS Soc* 2014;**17**(4 Suppl 3):19647.
14. Goedert JJ, Purdue MP, McNeel TS, et al. Risk of germ cell tumors among men with HIV/acquired immunodeficiency syndrome. *Cancer Epidemiol Biomarkers Prev* 2007;**16**(6):1266-9.
15. Siegfried N, Muller M, Deeks JJ, Volmink J. Male circumcision for prevention of heterosexual acquisition of HIV in men. *Cochrane Database Syst Rev* 2009;**15**(2):CD003362.

TAKE HOME MESSAGE

- Highly effective anti-retroviral therapies (ART) have shifted the management paradigm from AIDS defining illnesses to those of chronic diseases of ageing.
- Numerous benign urological conditions are more common in HIV affected patients, including UTI, prostatitis, Fournier's gangrene, renal dysfunction, erectile dysfunction and stone disease.
- One should maintain a high degree of suspicion in patients with urinary symptoms, but negative urine cultures, that they may have an atypical infection. HIV think TB; TB think HIV.
- Since the introduction of ART, AIDS defining cancers (ADC) have relatively decreased in incidence (apart from cervical and anal cancer), being replaced by non-ADC, now comprising 70% of diagnoses.



Mr Richard Cetti,

Consultant Urologist, Launceston General Hospital, Tasmania, Australia.

E: richcetti@hotmail.com

Declaration of competing interests:
None declared.



Prof John Lazarus,

Consultant Urologist, UCT, Division of Urology, Groote Schuur Hospital, Cape Town, South Africa.

Declaration of competing interests:
None declared.