

HIV infection in urological practice

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Abstract

The present review investigates the association between the presence of urological disorders and the transmission of human immunodeficiency virus (HIV). This study suggests that sexually transmitted infections (STIs) can increase the risk of infecting sexual partner or being infected with HIV. However, community-based STI control was not proved to be an effective HIV prevention strategy, although a few clinical trials revealed the possibility that aggressive treatment of STIs could decrease the transmission of HIV in specific population groups. Since the introduction of highly active antiretroviral therapy (HAART), HIV infection has become a chronic disease. Antiretroviral medications also were shown to be effective for the pre-exposure and post-exposure prophylaxis of HIV infection. Urologists should perform a critical role in preventing transmission of HIV by screening of HIV in the patients with urological disorders and using effective strategies to control the HIV epidemic.

Keywords: HIV infection, sexually transmitted infection, transmission, urology

Summary of recommendation

1. There is no definite evidence to prove that community- or population-based sexually transmitted infection (STI) control is an effective HIV prevention strategy (LoE 1a).
2. Immediate diagnostic evaluation and appropriate treatment of an individual with any symptomatic sexually transmitted infections (STIs) can reduce the risk of HIV acquisition (GoR B).
3. Prompt and effective treatment of HIV-infected individuals experiencing genital symptoms can limit the transmission of HIV (GoR B).
4. Male circumcision can be recommended for HIV prevention in men (LoE 1a; GoR A).
5. Interventions targeting people living with HIV are efficacious in reducing unprotected sex and acquisition of STIs (GoR B).
6. Short-term antiretroviral treatments, such as preexposure and postexposure chemoprophylaxis, are proved to reduce the risk of HIV transmission after exposure to HIV (LoE 1a; GoR A).

1 Introduction

Acquired immunodeficiency syndrome (AIDS) is an immune system disorder caused by human immunodeficiency virus (HIV) infection, and characterized by the development of various opportunistic infections, neoplasms, or other severe life-threatening conditions.

AIDS was a rapidly progressive and fatal disease in the early 1980s, however, the introduction of highly active antiretroviral therapy (HAART) in the Western world has dramatically improved survival and the quality of life for the HIV-positive patient, although AIDS remains the leading cause of death in many African cities [1], [2], [3], [4].

The three main modes of HIV transmission have changed little: unprotected intercourse, contact with blood, and transmission from mother to child [3]. Among them, HIV acquired through unprotected heterosexual intercourse is on the rise and considered to be a urological factor for HIV transmission. This review evaluates the scientific evidence suggesting that urological factors increase the efficiency of HIV transmission and discusses the important urological manifestations of HIV infection.

2 Methods

A systematic literature search and review of existing scientific evidence published in peer reviewed journals was performed in MEDLINE/PubMed for the period from 1 January 1986 to 31 December 2015 with the following key words: HIV transmission, sexually transmitted infection; and the following limitations: human, clinical trials, randomized controlled trials (RCTs), systemic review, meta-analysis, English. By the literature search and review, 2,223 articles were found and screened by the title and abstract of each electronic citation. We included clinical trials or review articles in which primary or secondary outcomes were HIV incidence or revealed risk of HIV transmission after any intervention for biomedical STI control. After clearly irrelevant articles were removed, 21 articles were obtained for full-text scrutiny. References from retrieved study reports and reviews were also screened for additional studies.

The studies were rated according to the level of evidence (LoE) and the grade of recommendation (GoR) using European Association of Urology (EAU) guidelines 2015 and ICUD standards (for details see Preface) [5], [6].

3 Epidemiology of HIV/AIDS

There were 36.9 million (34.3 million–41.4 million) people living with HIV in 2014. Since 2000, 38.1 million people have become infected with HIV and 25.3 million people have died of AIDS-related illnesses. Although the global percentage of people living with HIV has stabilized since 2000, the overall number of people living with HIV has increased as a result of ongoing number of new infections each year and the beneficial effects of highly active antiretroviral therapy (HAART). New HIV infections have fallen by 35% since 2000. The annual number of new HIV infections decreased from 3.1 million (3.0 million–3.3 million) in 2000 to 2.0 million (1.9 million–2.2 million) in 2014. The rate of new HIV infections has decreased globally, however, the number of new HIV infections in Middle East, North Africa, Eastern Europe, and Central Asia increased. Global efforts should be continued to prevent HIV transmission all over the world [2].

4 Dynamics of HIV transmission

Although HIV can be transmitted from person to person through HIV-infected blood, semen, vaginal fluids, and breast milk, sexual intercourse is the most common mode of HIV transmission. Sexual transmission accounts for 75 to 85 percent of HIV transmission [3], [4] and the risk of male to female transmission is much higher than that of female to male transmission [7], [8], [9]. The risk of female-to-male HIV transmission per episode of vaginal intercourse was estimated to be one in 700 to one in 3,000. In addition, the risk of male-to-female HIV transmission was estimated to be one in 200 to one in 2,000. The probability of HIV transmission per one episode of needle sharing with HIV-infected person was 0.67 percent (one in 150) [3].

Risk of HIV transmission varies depending on many systemic factors as well as local urogenital factors [3], [4], [7]. Differences in HIV infectiousness, host susceptibility, or differences in sexual behaviors can affect the spread of HIV infection. Factors that increase the concentration of HIV in genital tract secretions and in the blood may enhance the infectiousness of the HIV. As the viral loads of HIV-infected persons change according to the different stages of disease, the risk of HIV transmission is enhanced in primary infection or in later stages of HIV disease when the concentration of HIV is increased. It was known that the risk of HIV transmission was the greatest in people with acute HIV infection [3]. In a Ugandan population-based cohort, the adjusted rate ratio of HIV transmission per coital act was estimated by multivariate Poisson regression. The average rates of HIV transmission were 0.0082 and 0.0015/coital act within ~2.5 months and 6–15 months after seroconversion of the index partner, respectively [10]. In addition, the rate of HIV transmission 6–25 months before the death of the index partner was estimated to be 0.0028/coital act. As a result, early- and late-stage infection, higher HIV load, genital ulcer disease, and younger age of the index partner were shown to be significantly associated with higher rates of HIV transmission [10]. Furthermore, semen HIV viral burden influence on

heterosexual transmission. It was known that sexual transmission was unlikely to occur, at one per 10,000 episodes of intercourse, when HIV RNA in semen was low (<5,000 copies/mL) [11]. On the other hand, when the concentration of HIV in semen was above 1,000,000 copies/mL, the probability of HIV transmission were estimated to rise to three per 100 episodes of intercourse. Viral levels in the female genital tract and in semen correlate with systemic viral loads [12], [13], [14], although women may have detectable genital tract HIV-1 viral load even when their plasma HIV-1 RNA level is undetectable after receiving antiretroviral therapy. It is known that women with below detectable plasma HIV-1 RNA level may have less risk of HIV sexual transmission on a population level, but may continue to be possibly infectious on an individual level [15]. In fact, one of the most important determinants of genital viral loads is the presence of STIs [16], [17], [18]. It was also known that the concentrations of HIV in genital tract secretions from males and females were increased in patients with sexually transmitted infections (STIs) as well as in patients with acute HIV infection or the later stages of HIV infection [19], [20], [21], [22], [23]. In female patients with HIV infection, herpes simplex virus (HSV), human papillomavirus (HPV), *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Candida*, genital ulceration, bacterial vaginosis (BV) and vaginal discharge have been associated with increased HIV shedding [18]. In male patients with HIV infection, it was also reported that *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, cytomegalovirus (CMV), genital ulcer and urethritis were linked to HIV shedding in semen [18]. The dynamics of HIV infection can be influenced by the genetic characteristics of HIV-1. The biological characteristics of HIV-1 that are different for various HIV-1 subtypes may influence infectivity and transmissibility, the rate of disease progression, and the response to antiretroviral therapy (ART). Several research papers reported that the particular viral clade and circulating recombinant form (CRF) were found in some limited areas or limited population group with specific transmission pattern [24], [25], [26]. Several kinds of HIV-1 transmission routes associated with diverse risk behaviors have been noted in different regions of the world, and additionally it was reported that the HIV-1 epidemic in each region was caused by different subtypes [25]. In Thailand, the cocirculation of subtype B among intravenous drug users (IDUs) and CRF01_AE among heterosexuals was reported [27]. In South Africa, the segregation of subtype B to homosexuals and subtype C to heterosexuals was reported [28]. In Argentina, two concurrent epidemics have been reported, one among heterosexual men and women, is dominated by env subtype F, and the other among men who have sex with men, dominated by env subtype B [29]. Although the subtype B was the prevalent type in Europe, the progressive decrease in the transmission rate among IDUs and men who have sex with men and the parallel increase in heterosexual transmission introduced variants of non-B subtype into the Italian HIV-1 epidemic, which was also noted in other Western European countries [30], [31]. While the traditional risk groups such as homosexuals had high level of knowledge and avoided high-risk practices, the heterosexuals did not fully understand the importance of avoiding the HIV-related risk behaviors. Therefore, the increase in heterosexual transmission of HIV-1 between European partners and immigrants from non-Western countries, where non-B clades and CRFs were prevalent, introduced HIV-1 variants of non-B subtype in the Italian epidemic [31]. It was reported that the introduction and spread of different HIV-1 clade or recombinant viruses associated with the change of transmission pattern might influence the disease progression and the evolution of the HIV/AIDS epidemic [32].

5 Relative risk for specific exposure

Evidence studies for STIs as a risk factor of HIV transmission are summarized in table 1. Classic sexually transmitted diseases (STDs) (genital ulcers and mucosal inflammatory diseases) occur in the same geographic areas as HIV, and compelling epidemiological evidence supports the view that such diseases increase HIV transmission; indeed, the interaction between classic STDs and HIV is referred to as “epidemiological synergy” [16]. Several large RCTs were undertaken to investigate whether controlling STIs can reduce the incidence of HIV in a community. The first RCT enrolled 12,537 adults aged 15–54 years from six intervention communities and six pair-matched comparisons [33]. Baseline HIV prevalence was 3.8% and 4.4% in the intervention and control communities, respectively. There was a reduction in syphilis and symptomatic urethritis in the intervention group. The incidence of HIV infection was 1.2% and 1.9% in the intervention and control groups, respectively (odds ratio (OR) 0.58, 95% confidence interval (CI) 0.42–0.70), corresponding to a 38% reduction (95% CI 15–55%) in the intervention group. The intervention reduced both the incidence/prevalence of STIs and the incidence of

HIV infection. Since then, other trials in Rakai [34], [35] and Masaka [36] showed that there was no significant effect of STDs control on HIV prevention. Possible hypotheses have been suggested to explain these contrasting results. The relative contribution of individual STIs to an epidemic varies at different times and places depending on the maturity of the epidemic and the relative prevalence of HIV and STI infection in the community [37]. Although they did not show a reductions in HIV acquisition, there were reductions in adverse other outcomes such as neonatal mortality. A cluster-randomized trial in Zimbabwe also showed that STI management did not reduce population-level HIV-1 incidence in a declining epidemic [38]. In systemic review of Cochrane Database, no evidences were found proving that control of STIs could reduce HIV incidence at the population or community level [39]. In addition, Gray and Wawer expressed concern that the policy to control STIs as a general HIV-prevention strategy might waste scarce resources which could be used for the other proven efficacious interventions [40]. However, O'Farrell suggested the possibility that relaxation of STI control could lead to increased STI rates and enhanced HIV transmission [41].

Table 1: Evidence table for studies of sexually transmitted infections (STIs) as risk factor of both HIV transmission and acquisition that include original data, systematic reviews, meta-analysis, or other human data (1986–2015).

Study type	STI type	Leader author, year, reference	Design	Level of Evidence (LoE) Positive (role of a risk factor) or Negative
Systematic reviews, meta-analysis and modeling				
	STIs	Sangani, 2004 [121]	Systematic review and meta-analysis of the five RCTs	1, Positive
	STIs	Hay, 2008 [37]	Systematic reviews	1, Positive
	STIs	Ng, 2011 [122]	Sytematic review and meta-analysis of the four RCTs	1, Negative
	Bacterial vaginosis	Atashili, 2008 [123]	Systematic review and meta-analysis of the 23 eligible publications	2, Positive
Randomized-controlled trials				
	STIs	Grosskurth, 1995 [33]	12,537 adults aged 15–54 in six intervention communities and six pair-matched comparisons communities in Mwanza, Tanzania	1, Positive
	STIs	Wawer, 1999 [34]	12,726 adults aged 15–59 in Rakai, rural Uganda	1, Negative
	STIs	Gray, 2001 [35]	2,070 pregnant women in Rakai, Uganda	1, Negative
	STIs	Kamali, 2003 [36]	12,819 individuals aged 13 and older in Masaka, rural Uganda	1, Negative
	STIs	Gregson, 2007 [38]	11,980 individuals in Zimbabwe	1, Negative

Study type	STI type	Leader author, year, reference	Design	Level of Evidence (LoE) Positive (role of a risk factor) or Negative
	CMV	Casper, 2008 [51]	16 HIV-positive men and 10 HIV-negative men in Seattle, USA	1, Positive
Non-randomized cohort studies				
	Genital ulcers	Cameron, 1989 [124]	Prospective study of 422 men who had acquired STD from female CSWs in Nairobi	2, Positive
	Genital ulcers, <i>Chlamydia trachomatis</i>	Plummer, 1991 [125]	124 seronegative female CSWs in Nairobi	2, Positive
	<i>Neisseria gonorrhoeae</i> , <i>Chlamydia trachomatis</i> , <i>Trichomonas vaginalis</i>	Laga, 1995 [126]	Cohort study of 431 HIV-negative female CSWs in Kinshasa, Zaire followed for 2 years	2, Positive
	Bacterial vaginosis	Taha, 1998 [127]	1,296 antenatal pregnant and 1,169 postnatal seronegative women in Malawi	2, Positive
	Bacterial vaginosis	Martin, 1999 [128]	657 seronegative female CSWs in Kenya	2, Positive
	Bacterial vaginosis	Myer, 2005 [129]	410 women screened for cervical cancer in South Africa	2, Positive
	CMV	Sheth, 2006 [49]	26 HIV-infected MSMs and 15 uninfected controls (6 MSMs; 9 heterosexuals) in Toronto, Canada	2, Positive
	HSV-2	Rebbapragada, 2007 [44]	55 HIV-infected and 36 uninfected female CSWs in Nairobi, Kenya	2, Positive
Case-control studies				
	Urethritis	Cohen, 1997 [130]	135 HIV-1-seropositive men in Malawi	3, Positive
	<i>Neisseria gonorrhoeae</i> , <i>Chlamydia trachomatis</i> , genital ulcers	Ghys, 1997 [131]	609 HIV-1-seropositive women in Abidjan, Cote d'Ivoire	3, Positive
Case-series				
	HSV, syphilis	Stamm, 1988 [132]	200 homosexual men with acute proctitis and 111 asymptomatic homosexuals	3, Positive

Study type	STI type	Leader author, year, reference	Design	Level of Evidence (LoE) Positive (role of a risk factor) or Negative
<p><i>The hierarchy of study types was: systematic reviews and meta-analysis of randomized controlled trials, non-randomized cohort studies, case-control studies, case series, and expert opinion (as the lowest level).</i></p>				

In Burkina Faso, a randomized, double-blind, placebo-controlled trial of herpes simplex virus (HSV) suppressive therapy with valacyclovir was undertaken among women who were seropositive for HIV-1 and HSV-2 [42]. All were ineligible for highly active antiretroviral therapy and followed for 24 weeks with 12 weeks before and 12 weeks after randomization. Valacyclovir therapy was found to be associated with a significant decrease in the frequency of genital HIV-1 RNA (OR 0.41, 95% CI 0.21–0.80) and in the mean quantity of the virus (log₁₀ copies per milliliter -0.29, 95% CI -0.44–0.15). Genital herpes infection is now thought to be the most important cofactor in mature epidemics of HIV [37]. HSV-2 was known to drive secondary transmission of HIV from HSV2-HIV co-infected persons [43]. Rebbapragada et al. [44] conducted a well-defined cohort study among 55 HIV-infected and 36 uninfected Kenyan female commercial sex workers (CSWs). HSV-2 shedding is much more common in HIV-infected than HIV-uninfected women, perhaps due to HIV-induced depletion of mucosal immature dendritic cells exerting local HSV-2 immune control. In other clinical trials among HIV-1, HSV-2 co-infected persons, it was reported that HSV-2 suppression with acyclovir reduced the risk of HIV-1 disease progression [45], [46]. However, in one study of heterosexual HIV-1-serodiscordant couples among the partners who were infected with both HIV-1 and HSV-2, treatment with acyclovir for the suppression of HSV-2 infection did not decrease the transmission rate of HIV-1 to the uninfected partners, although acyclovir treatment reduced significantly plasma HIV-1 RNA levels and the incidence of genital ulcer disease [47].

Human cytomegalovirus (CMV), HSV-2, *Neisseria gonorrhoeae*, and other STIs can act as an important cofactor enhancing HIV secondary transmission either by breaching the epithelial barrier, recruiting HIV target cells to the genital tract, or by generating a pro-inflammatory local immune milieu [48], [49]. It was suggested that decreasing CMV transmission prenatally and postnatally might decrease the risk of HIV transmission among HIV-exposed-uninfected infants [50]. Sheth et al. [49] enrolled 26 chronically HIV-infected men who have sex with men (MSMs) and 15 HIV-uninfected men (six MSMs; nine heterosexuals). CMV shedding was associated with a 10-fold increase in HIV levels in semen, independent of HIV blood viral load CD4+ T cell count, and there was a strong linear correlation between the semen levels of HIV RNA and CMV DNA. In the US RCT trial, a total of 16 HIV-positive men and 10 HIV-negative men with HHV-8 were randomized to receive 8 weeks of valganciclovir or 8 weeks of placebo administered orally. Valganciclovir reduced oropharyngeal shedding of HHV-8 and CMV [51]. Several randomized controlled trials showed that male circumcision significantly reduced the risk of HIV acquisition in men in Africa [52]. Lack of male circumcision [53], [54], [55] can be considered as a facilitating factor or high levels of male circumcision and condom use can be considered as protective factors (please refer to the chapter on male circumcision). Facilitating factors are virtually all positively correlated with high-risk sex behaviors and are essential for epidemic HIV transmission, but they are difficult to quantify. Anal intercourse poses a higher risk of HIV transmission compared with vaginal intercourse because of the greater amount of tissue trauma that may occur [56], [57].

6 Screening for STIs

STIs facilitate both transmission and acquisition of HIV with relative risks of 2 to 5 [16]. Presence of any symptoms or signs suggestive of STIs should prompt immediate diagnostic evaluation and

appropriate treatment. Because STIs are frequently asymptomatic, routine laboratory screening for STIs should be undertaken in high-risk populations where resources are available [58].

7 HIV counseling and testing

Since the first diagnostic HIV test in 1985, HIV testing has become easier, more sensitive, more accessible and less invasive. Unfortunately, national data indicate that a large percentage of new human immunodeficiency virus (HIV) diagnoses are made in the late stages of disease. In the United States, 40% of patients with newly diagnosed HIV infection develop AIDS within one year of testing. Furthermore, it has been estimated that one-fourth of the people living with HIV infection in the United States do not know they are infected and, thus, miss the opportunity to receive life-saving antiretroviral therapy [26], [27], [59]. That lack of awareness of HIV infection is critical from the public-health perspective as it is estimated that over 50% of new sexually transmitted HIV infections are due to people unaware of their HIV infection; and evidence strongly suggests that once individuals are made aware of their infection, they reduce their risk behavior and decrease the probability of transmitting infection [60]. In addition, people with acute HIV infection (which is defined as the first three weeks of infection) or early infection (the first six months) represent the greatest risk for transmission [3]. Therefore, HIV testing provides an opportunity for decreasing the continued incidence of HIV infection and for providing life-saving therapy to newly diagnosed patients. To decrease the number of people unaware of their HIV infection, in 2006, the Center for Disease Control and Prevention (CDC) expanded its HIV-testing recommendations [61]. The new CDC recommendations advocate voluntary “opt-out” HIV screening in healthcare settings for all adults instead of just screening traditionally “high-risk” patients. The recommendations also suggest eliminating requirements for written consent for HIV testing, annual re-testing for persons with known risk factors, and third-trimester screening for women who test negative for HIV early in pregnancy.

To date, the enzyme immunoassay (EIA) format is still the primary HIV antibody screening test in most settings. Assays are available to assess HIV-1 and HIV-2 separately or in combination [62]. The recent introduction of alternative fluids as suitable samples has allowed testing to go beyond the clinic setting. Oral fluid (mucosal transudate) testing is a valuable tool for outreach projects [63]. These noninvasive sample collections such as oral fluid and urine tend to decrease the chance of occupational exposure among health care workers.

8 Highly active anti-retroviral therapy (HAART)

The effects of anti-retroviral therapy have been assessed by using the surrogate markers such as plasma HIV viral load and CD4 cell count [64], [65]. Anti-retroviral combination therapy with two nucleoside analogues was shown to be superior to treatment with zidovudine monotherapy for slowing the progression of HIV disease [66]. In addition, it was reported that profound suppression of HIV replication could be obtained by the triple combination anti-retroviral therapy [67], [68]. The use of three or more anti-retroviral drugs is known as highly active anti-retroviral therapy (HAART). If only one drug was taken, HIV could quickly become resistant to it and the drug would stop working. Taking two or more anti-retrovirals at the same time vastly reduces the rate at which resistance might develop, making treatment more effective in the long-term [69]. There are more than 25 anti-retroviral drugs in 6 mechanistic classes, which are approved by Food and Drug Administration (FDA) for treatment of HIV infection (Table 2). Six classes of anti-retroviral agents are grouped by how these agents inhibit HIV replication and include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), a fusion inhibitor (FI), a CCR5 antagonist, and integrase strand transfer inhibitors (INSTIs). The initial HAART regimens usually consist of two NRTIs, plus a drug from one of three ARV classes: an INSTI, an NNRTI, or a PI. Several clinical trials and studies have showed HIV RNA decreases and CD4 T lymphocyte cell increases in HIV-infected patients who received HAART [70], [71], [72], [73]. Advances in antiretroviral therapy have made a change in HIV from an almost uniformly fatal disease to one that is a manageable chronic illness requiring continued evaluation and therapy.

74]">

Table 2: FDA-approved antiretroviral drugs for treating HIV/AIDS [74]

Anti-retroviral drug class	Abbreviation	Generic name	Mechanism of action
Nucleoside/Nucleotide reverse transcriptase inhibitors (NRTIs, nucleoside analogues)	3TC	lamivudine	NRTI interfere with the action of an HIV protein called reverse transcriptase, which the virus needs to make new copies of itself.
	ABC	abacavir	
	AZT or ZDV	zidovudine	
	d4T	stavudine	
	ddC?	zalcitabine?	
	ddl	didanosine	
	FTC	emtricitabine	
	TDF	tenofovir	
Non-nucleoside reverse transcriptase inhibitors (NNRTIs, non-nucleosides)	DLV	delavirdine	NNRTIs also stop HIV from replicating within cells by inhibiting the reverse transcriptase protein.
	EFV	efavirenz	
	ETR	etravirine	
	NVP	nevirapine	
	RPV	rilpivirine	
Protease inhibitors (PIs)	APV	amprenavir?	PIs inhibit protease, which is another protein involved in the HIV replication process.
	FOS-APV	fosamprenavir	
	ATV	atazanavir	
	DRV	darunavir	
	IDV	indinavir	
	LPV/RTV	lopinavir/ritonavir	
	NFV	nelfinavir	
	RTV	ritonavir	
	SQV	saquinavir	
	TPV	tipranavir	
Integrase strand transfer inhibitors (INSTIs)	RAL	raltegravir	Integrase inhibitors interfere with the integrase enzyme, which HIV needs to insert its genetic material into human cells.
	DTG	dolutegravir	
	EVG	elvitegravir	
Entry inhibitors	MVC	maraviroc	Entry inhibitors prevent HIV from binding to or entering human immune cells.
Fusion inhibitor	T-20	enfuvirtide	Fusion inhibitors prevent the binding, fusion, and entry of HIV to human cells

9 Urological manifestations of HIV infection

HIV infection in either early or late stages affects each of the major organs in the genitourinary system.

9.1 Urinary tract infections

The risk of bacterial and opportunistic infection, including urinary tract infections (UTIs), rises dramatically when the CD4 cell counts fall below $500/\text{mm}^3$ [75], [76]. The most common bacterial pathogens in HIV-infected patients are *Escherichia coli*, *Enterobacter*, *Pseudomonas aeruginosa*, *Proteus spp.*, *Klebsiella*, *Acinetobacter*, *Staphylococcus aureus*, *Group D Streptococcus*, *Serratia*, and *Salmonella spp.* [76], [77], [78], [79], [80]. Atypical pathogens including fungi (*Candida albicans*, *Aspergillus*, *Blastomyces*, *Cryptococcus neoformans*, *Cryptosporidia*, *Histoplasma capsulatum*), parasites (*Toxoplasma gondii*, *Pneumocystis carinii*), mycobacteria (*Mycobacterium tuberculosis*, *Mycobacterium avium complex*), and viruses (cytomegalovirus and adenovirus) are often widely disseminated in patients with very low CD4 cell counts (usually $<100/\text{mm}^3$) [79], [80], [81], [82], [83]. They may potentially affect any portion of the genitourinary tract, including the adrenals, kidneys, bladder, prostate, testes and epididymides. When urinary cultures from 98 HIV-infected men were collected prospectively at six-monthly intervals over two years, and when they had signs and symptoms of UTI, one or more positive urinary cultures were found in 30% whose CD4 cell count was $<200/\text{mm}^3$ and in 11% with a CD4 cell count of $200\text{--}500/\text{mm}^3$. No bacteriuria or symptomatic infective episodes were found in those with CD4 cell counts of $>500/\text{mm}^3$ [75]. In autopsy studies of patients with AIDS, renal tuberculosis was identified in 6–23%. Although most of these patients had symptoms and signs of pulmonary tuberculosis, 20% had subclinical disease. The clinical diagnosis is made with urine tuberculosis culture, excretory urography, cystoscopy and biopsy with staining for acid-fast bacilli. Treatment requires at least three and sometimes four agents, including rifampicin, isoniazid, pyrazinamide and ethambutol for six to nine months, depending on sensitivity results [76], [79]. The incidence of acute bacterial prostatitis is 1% to 2% in the general population, whereas it is 3% in asymptomatic, HIV-infected patients and 14% in patients who have AIDS [84]. The incidence of prostatic abscesses in AIDS has decreased significantly with the advent of HAART, because they occur only in patients with very low CD4 cell counts [77]. In autopsy studies of patients with AIDS and systemic opportunistic infections, the prevalence of concomitant testicular infection is 25–39%. The causative organisms include *Salmonella*, Cytomegalovirus (CMV), *Mycobacterium avium intracellulare* (MAI), *Toxoplasma*, *Histoplasma* and *Candida albicans* [80], [85].

9.2 Malignancies

Many malignancies occur in HIV-infected patients. Possible mechanisms proposed that support malignancy formation include decreased immune surveillance, a direct effect of viral proteins, cytokine dysregulation, other immunologic factors, or viral cofactors [86], [87]. Vascular and lymphoreticular malignancies have been associated most strongly with HIV infection, particularly Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL). The risk of KS and NHL are increased 1,000- and 100-fold, respectively, among HIV-infected patients compared with the general population [88]. KS, systemic intermediate/high-grade B-cell NHL, and invasive cervical cancer are considered to be AIDS-defining malignancies. Many non-AIDS-defining malignancies have, however, also been found in greater frequency among those with HIV, including germ cell testicular tumors, renal cell carcinoma, and prostate cancer [89]. HAART radically changed the clinical spectrum of HIV infection in industrialized countries. The incidence of AIDS-associated malignancies decreased significantly after the introduction of HAART [90]. Systemic NHL incidence decreased less than KS and later than the other AIDS-defining illnesses. Consequently, lymphoma has become the most common AIDS-associated malignancy among patients receiving HAART [91]. KS can present as a systemic disease that affects internal organs, including the kidneys and testes [92], [93]. A herpes virus, called KS herpes virus or human herpes virus type 8, transmitted by sexual contact or through blood may be related to the development of KS in the HIV-positive population [77], [81]. Genital lesions appear in approximately 20% of patients who have KS, with $<3\%$ having the initial lesions on the penis [94]. Renal involvement of NHL in patients who have AIDS is 6% to 12%, and presentation may be bilateral [77], [79]. Renal cell carcinoma carries an 8.5-fold greater risk for HIV-infected patients compared with non-infected patients [95]. Retrospective

review of 3,000 patients enrolled in an HIV clinic found a 50 times greater rate of testicular malignancy in the general population [96]. Compared with HIV noninfected patients, there is a greater risk of tumor bilaterality and a greater risk of high-grade testicular lymphoma [97]. Recently, Vianna and colleagues [98] examined a cohort of 534 men aged 49 years and older who had risk factors for HIV. Among older men, prostate-specific antigen (PSA) levels increased with age but did not differ by HIV status. The study recommended that standard PSA evaluations can be made with HIV-positive patients without the need for adjustments. HIV infection is associated with human papillomavirus (HPV)-related anogenital malignancies. HPV types 16 and 18 are considered high risk in anogenital malignancy formation of carcinoma in situ and squamous cell carcinoma [99]. Bowen's disease (Carcinoma *in situ*) of the penis, considered a premalignant lesion, appears more common in the HIV-infected population [100].

9.3 HIV-associated nephropathy (HIVAN)

HIV-associated nephropathy (HIVAN) is the most well-known and aggressive kidney disease in HIV-infected patients. With the widespread use of HAART, its prevalence is declining in industrialized countries [101]. The prevalence of HIVAN is reported to be 3.5% in HIV-infected clinic patients and 6.9% in autopsy series of HIV-infected patients [102]. Scientific evidence suggests that HAART can prevent the development of HIVAN [103], [104], [105]. Therefore, all patients with HIVAN should receive HAART. In addition, standard therapy for chronic kidney diseases are recommended for persons with HIVAN, including control of blood pressure, the use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers for the purpose of delaying disease progression or the need for renal replacement therapy [104], [105], [106]. HIV infection and related antiviral therapies are associated with diverse renal pathology, glomerular diseases, tubular injuries owing to tenofovir therapy, metabolic syndrome, obesity, and diabetic nephropathies. Clinicians should perform periodic screening of renal function and the possibility of HIV-associated glomerular or tubular diseases [105], [106].

9.4 Voiding dysfunction

Of patients with AIDS, 30-40% have neurological involvement, and in 20% this is the initial manifestations. In HIV-infected patients who present with voiding disturbances, an underlying neurological cause is present in 60%, and 90% of those already have AIDS-associated infections or tumors [79]. Urinary retention is the most common voiding dysfunction (54%) seen by urologists, although detrusor hyperreflexia (27%) and outflow obstruction (18%) have been documented during urodynamic study of AIDS patients with voiding symptoms [107], [108]. Voiding complaints often reflect the degree of systemic impairment and poor prognosis, although such symptoms often improve substantially after effective antiretroviral therapy [79].

9.5 Other urological manifestations

Several complications related to HAART such as urolithiasis and sexual dysfunction have been reported. The strongest association is with protease inhibitors, especially indinavir and atazanavir, and more recently darunavir [109]. Therefore, physicians should try to reduce the incidence of antiretroviral-induced nephrolithiasis by performing close surveillance of patients on long-term antiretroviral therapy [110]. Several studies have reported that 10-28% of patients receiving indinavir may develop a new form of urinary stones, known as "indinavir urolithiasis" [109], [110], [111], [112]. Pure indinavir stones are radiolucent and cannot be detected with either conventional radiography or CT. However, mixed stones consisting indinavir and calcium oxalate or phosphate salts have occasionally been reported in HIV-positive patients [113]. This adverse effect may be managed by the discontinuation of indinavir administration, urine acidification, hydration, alpha-blockers to facilitate stone passage, as well as the possible early insertion of bilateral double-J ureteral stents [114]. HAART, especially protease inhibitor-based therapy, also plays a role in sexual dysfunction [115], [116].

In a cohort study [117], the incidence of erectile dysfunction and decreased libido in HIV-positive homosexual men is 26%. In that study, in patients who were taking HAART, the incidence of reduced

libido was 48% and the rate of erectile dysfunction was 25%. Decreased libido may be a result of raised estradiol level, low testosterone level, fatigue, depression and hypogonadism. However, Lallemand et al. [118] oppose the occurrence of sexual dysfunction in HIV-positive men taking protease inhibitors in their cross-sectional study. In another study, it was said that there was no association between erectile dysfunction or hypogonadism with the use of anti-retroviral medications [119]. Phosphodiesterase type-5 (PDE-5) inhibitors used for the treatment of erectile dysfunction also may interact with protease inhibitors, which increase the blood concentrations of PDE-5 inhibitors. Starting PDE-5 inhibitors at a lower dose with a caution for side-effect may be more appropriate in patients taking protease inhibitors [120].

10 Further research

Community-based RCTs or other clinical trials should test a range of alternative STI control strategies in a variety of different clinical settings in the future. Improved trials – especially more detailed estimates that measure a range of factors that include health seeking behavior and quality of treatment, as well as HIV, STI and other biological endpoints – will help us to identify the best possible intervention strategies for preventing the spread of HIV infection.

11 Conclusions

The current world-wide expansion of the AIDS epidemic is primarily driven by the sexual transmission of HIV. Evidence from intervention studies indicates that in the presence of other STIs, individuals are more likely to acquire HIV if exposed to the virus through sexual contact. Therefore, early detection and treatment of curable STIs can play a vital role in comprehensive programs to prevent sexual transmission of HIV. However, there is limited evidence from randomized controlled trials that control of STIs reduce HIV incidence at a population level. HIV both primarily and secondarily affects virtually every part of the genitourinary system. The availability of HAART has resulted in prolonging time to development of AIDS and improving AIDS survival rates. Urologists who treat genitourinary manifestations of HIV infection face a significant challenge in trying to restore and maintain normal genitourinary function.

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