SEXUAL MEDICINE REVIEWS

HIV and Men

Haci Ibrahim Cimen, MD,[1] Arie Stewart Parnham, MBChB, FRCS (Urol),[2] and Ege Can Serefoglu, MD, FECSM[3]

ABSTRACT

Introduction: Since the initial description of HIV and AIDS, monumental efforts have been made both in the developed and developing countries to devise strategies and medications to control the disease. The advent of highly active antiretroviral therapy has now meant that the diagnosis of HIV is no longer a life-sentence and compliant patients with HIV can expect life expectancy similar to their noninfected peers. Consequently new challenges have arisen in the management of benign conditions.

Aim: To provide an overview of the key conditions and issues that HIV/AIDS patients may present with to an andrological service.

Methods: Using PubMed, we screened the literature for studies on common andrological conditions specifically pertaining to HIV and AIDS.

Main Outcome Measures: The urological manifestations of HIV/AIDS in men have been summarized in an attempt to provide a useful guide for sexual health practitioners dealing with HIV-positive men.

Results: As a result of advancements in pharmaceuticals, life expectancy of men infected with HIV has improved almost to that of the general population in developed countries. Therefore, clinicians are faced with non—life-threatening urological problems that affect the quality of life of men with HIV. The majority of these problems can be managed easily, by adapting a "patient-centered" approach, instead of "disease-centered" algorithms.

Conclusion: With improved survival and understanding, patients with HIV/AIDS can and do expect to enjoy a healthy sex life. With appropriate counseling around safe sex and careful management with consideration for disease-specific issues as well as the influence of medical therapy, patients can achieve a good quality of life.

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Key Words: AIDS; Erectile Dysfunction; HIV; Sexual Dysfunction; Sexually Transmitted Disease

INTRODUCTION

HIV is a lentivirus (a subgroup of retrovirus) that is estimated to affect 30.6 to 36.1 million people worldwide, the vast majority of whom are located in sub-Saharan Africa.[1] The virus is carried by most bodily fluids, although transmission is only convincingly possible by blood, semen, and vaginal secretions.[2] Once the virus gains access to its host it binds to the CD4 molecule on T4 lymphocytes among other cells. It is able to incorporate its own RNA into the host cells' DNA via reverse transcriptase. The cell then replicates the incorporated DNA into viral mRNA, which is then released. The effect is that of a reduction in the CD4 exhibiting immune cells and if left unchecked, collapse of the host's immune system. Patients with HIV can go on to develop AIDS. A patient is considered to have progressed to AIDS if their CD4 count is <200 cells/mm^3 or they exhibit 1 of >20 AIDS defining conditions.[3]

Prior to the introduction of modern therapies, HIV inevitably progressed to AIDS and ultimately death.[4] Management was primarily focused on the treatment of opportunistic infections and malignancies and ignored the treatment of nonlethal conditions such as voiding dysfunction or sexual disorders. However, with the introduction of antiretroviral therapy (ART) and highly active antiretroviral therapy (HAART), the mortality associated with the disease has progressively reduced and patients can expect to live longer than 20 years if fully compliant.[5] As a consequence patients are developing more infectious, oncologic, endocrinologic, and metabolic comorbidities[6] related to HIV or long-term use of ART.[7,8] In addition to HIV-associated infectious diseases and malignancies, body fat redistribution, metabolic syndrome, an

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[1]Sakarya University Hospital, Department of Urology, Sakarya, Turkey;

[2]Manchester Royal Infirmary, Manchester, United Kingdom;

[3]Bagcilar Training & Research Hospital, Department of Urology, Istanbul, Turkey

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impaired hypothalamic-pituitary-gonadal axis, and sexual disorders also can affect patients' quality of life and cause serious problems.[9,10] Consequently the emphasis of management has shifted.

This article aims to summarize the urological manifestations of HIV/AIDS in men in an attempt to provide a useful guide for sexual health practitioners dealing with HIV-positive men.

SEXUALLY TRANSMITTED INFECTIONS

A number of studies have demonstrated that the presence of a sexually transmitted infection (STI) increases the risk of HIV transmission and acquisition.[11–18] Accurate diagnosis and treatment of STIs are of importance in individuals at high risk for HIV infection. Anyone with an STI or at risk for STIs should be recommended for HIV testing after appropriate counseling.[19] These infections may have more atypical and prolonged clinical manifestations in people with HIV infection.[19]

Genital Herpes Virus

Herpes simplex virus (HSV) infection is common in HIV-infected patients, with HSV-2 being predominant.[20] In the HIV population, HSV types 1 and 2 cause recurrent, severe, painful vesicles with an erythematous base.[21] Untreated lesions may enlarge and develop into confluent ulcerations that persist with secondary bacterial infections. Sometimes unusual ulcerations can occur without well-defined vesicles.[21] Herpes vegetans can present as an exophytic lesion associated with HSV and can easily be mistaken for penile cancer or condyloma.

Specific diagnosis is established by viral culture, polymerase chain reaction, or biopsy. It is understood that HSV infection increases HIV replication in patients infected with both viruses.[22] Although anti-HSV treatment with acyclovir reduces HIV in genital secretions among HIV and HSV—coinfected patients, randomized clinical trials have found that acyclovir as HSV suppressive therapy did not decrease the incidence of HIV infection in HSV-positive, HIV-negative women.[23,24]

Human Papillomavirus

In HIV-positive patients, the human papillomavirus (HPV) may cause warts in unusual locations such as the lip, tongue, and oral mucosa, in addition to the genitalia.[21] These lesions are resistant to treatment and these patients may be at higher risk of recurrence.[19] Whenever extensive warts develop, the patient should be screened for HIV infection.

HPV and HIV infection increases the risk for penile cancer by 5.9 and 8 times, respectively, compared to those without.[25] In part the increased risk of penile caner in HIV-positive men is a function of the increased risk of HPV in this group. However, there is evidence to suggest there is a synergistic relationship between HIV and HPV in the development of penile cancer.[26]

There is also an increased risk of anal cancer in HIV-infected patients who have had receptive anal intercourse and consequently some authorities recommend cytology for screening anal squamous intraepithelial neoplasia.[19]

Syphilis

A high prevalence of syphilis is found in men who have sex with men (MSM) in HIV-infected populations.[19,27] Primary infection with *Treponema pallidum* presents as the typical chancre in HIV-infected patients. Secondary syphilis may present in classic papulosquamous form with the involvement of palms, soles, and mucous membranes. However, unusual presentations are common, such as verrucous plaques, extensive oral ulcerations, keratoderma, deep cutaneous nodules, and widespread gummata.[21] The disease may progress faster from secondary to tertiary syphilis in HIV-infected patients. Early central nervous system relapse also can be more common.[28]

Chancroid

Chancroid is a cofactor for HIV transmission.[29] Culture of *Haemophilus ducreyi* is needed for definitive diagnosis.[30] A probable diagnosis can be made if the patient has painful genital ulcers, no evidence of *Treponema pallidum* infection, and a negative test for HSV.[28] The combination of painful ulcer and tender inguinal adenopathy suggests a diagnosis of chancroid. When accompanied by suppurative inguinal adenopathy, these signs are almost pathognomonic.[28]

Urethritis

Reiter syndrome, which consists of uveitis, urethritis, and arthritis, is the first rheumatic disease reported in HIV-positive patients and often presents in incomplete form.[31] The relation between Reiter syndrome and AIDS is poorly understood. The syndrome, and particularly the urethral discharge are usually refractory to antibiotic therapy.

Molluscum Contagiosum

Molluscum contagiosum is caused by a sexually transmitted poxvirus and develops in 10% to 20% of AIDS patients.[21] Characteristic lesions are umbilicated, dome-shaped, translucent 2- to 4-mm papules.[21] Lesions are widespread and may attain immense size in AIDS patients.[32] Most HIV-infected patients with extensive molluscum contagiosum have CD4 counts <250 cells/mL.

GENITOURINARY TRACT INFECTIONS IN HIV-INFECTED MEN

Urinary Tract Infections and Renal Infections

In patients with a CD4 count <200 cells/μL or with a high viral count urinary tract infections can be common, with the most usual organism being *Escherichia coli* and gram-negative Enterobacteriaceae. However, other atypical pathogens can be

Table 1. Examples of Atypical Urinary Tract Infections

Fungi	Parasites	Mycobacterium	Viruses
Candida albicans, Aspergillus spp, Blastomyces, Cryptococcus neoformans, Cryptosporidia, and Histoplasma capsulatum	Toxoplasma gondii and Pneumocystis jirovecii	Mycobacterium tuberculosis and Mycobacterium avium complex	Cytomegalovirus Adenovirus

isolated, as listed in Table 1. The presentation of both renal and lower urinary tract infections can be unusual. Investigations should be tailored and a high level of suspicion for uncommon pathologies such as renal abscesses and emphysematous pyelonephritis should be adopted. As with any infection, the key to management is the initiation of organism-specific therapy, which can only be achieved with appropriate culture. Therefore, normal culture should be sent alongside cultures for urinary tuberculosis or PCR-based assays where clinical suspicion dictates.

Prostatitis

The prostate is the site for varied opportunistic infections, including fungal species in HIV-infected men. Bacterial prostatitis was found in 8% of men hospitalized for HIV.[33] The clinical presentation includes fever, obstructive and storage voiding symptoms, and a tender prostate on digital rectal examination with or without fluctuance. Superimposed urinary tract infections occur in 22% of AIDS patients.[34] A broad culture including aerobes, anaerobes, fungi, and mycobacteria is required for diagnosis. Treatment is based on rehydration and the use of a correctly selected antibiotic based on culture sensitivities. In cases in which prostatitis is complicated by a prostatic abscess treatment, options include medical management, or open, transrectal, or endoscopic drainage.

Epididymitis and Orchitis

Testicular atrophy secondary to endocrine imbalances, febrile episodes, malnutrition, toxic effects of therapeutic agents, and testicular infections are the most common intrascrotal pathology in AIDS.[35] Opportunistic testicular infection can be seen in up to 39% of AIDS patients in autopsy series.[36] Most patient testes exhibited marked spermatogenic arrest, germ cell degeneration, peritubular fibrosis, and Leydig cell depletion, that likely reflect severe systemic disease.[37] Unusual organisms such as *Candida* spp and cytomegalovirus can cause epididymitis in immunosuppressed patients.[38,39] Immunosuppressed patients may be less likely to respond to medical

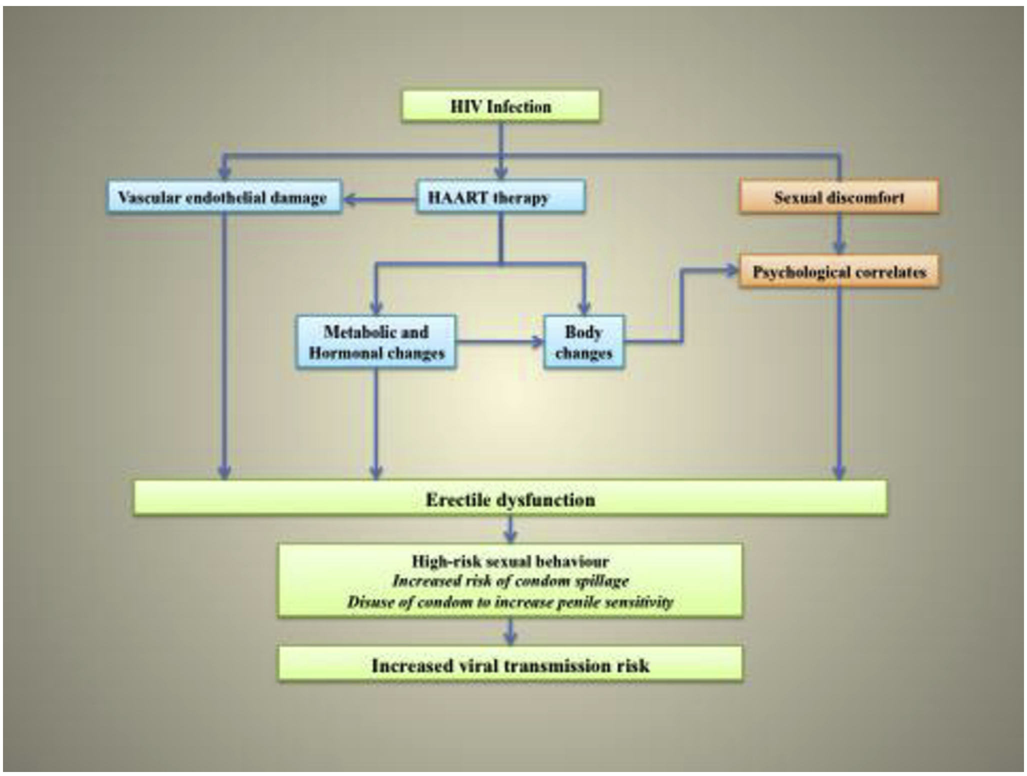

Figure 1. Pathological and psychological factors affecting ED pathogenesis in men with HIV.

Table 2. Factors Contributing to ED in Men With HIV

Classic Component of ED
Age
Hypogonadism
Metabolic syndrome
Obesity
Diabetes mellitus
Dyslipidemia
Hypertension
Endothelial dysfunction
Lifestyle
Alcohol, drug, or substance abuse
HIV-Specific Components of ED
Body image and self-perception changes related to lipodystrophy
HIV-related psychological issues
• Fear of virus transmission
• Depression
• Anxiety
• Lower self-esteem
HIV-related sexual issues
• Sexual orientation and partner references
• Obligatory condom use
HAART
• HAART-related comorbidities due to classic components of ED
• Body image changes
Medications also prescribed to patients with HIV
• Antidepressants
• Anxiolytic
• Antipsychotic drugs

ED = erectile dysfunction; HAART = highly active antiretroviral therapy.

therapy and require prolonged courses of antibiotic therapy or require surgery.[40]

Fournier Gangrene

Fournier gangrene is a necrotizing fasciitis of the perineal genitalia or perianal area caused by synergistic polymicrobial infections and has a propensity to occur in immunocompromised hosts.[41] This aggressive, progressive, necrotizing fasciitis can be the presenting finding in previously undiagnosed AIDS patients.[42] Initial management depends on rapid diagnosis with a low index of suspicion, wide surgical debridement, hemodynamic support, and prolonged antibiotic therapy.

VOIDING DYSFUNCTION

HIV affects both the central and peripheral nervous systems and may cause voiding dysfunction in the advanced stage of the disease.[43] HIV encephalitis, AIDS-related dementia, cerebral toxoplasmosis, CMV polyradiculopathy, and disorders of demyelination are commonly seen in advanced stages of the disease.[44] Neurogenic voiding dysfunction directly related to AIDS carries a 40% mortality within 8 months and is thus an indicator of poor prognosis.[43] Urinary retention (54%) is the most common voiding symptom, whereas detrusor overactivity (27%) and outflow obstruction (18%) have been documented during urodynamic evaluation of AIDS patients with voiding symptoms.[45,46] Lower urinary tract symptoms due to benign prostate hyperplasia can be worsened with HIV infection, particularly in elderly patients.

Management reflects that of patients without HIV; however, urinary catheters for storage problems are best avoided due to the increased risk of sepsis in immunocompromised patients.

TESTICULAR CANCER

The incidence of testicular cancer is 50 times greater in the HIV population in comparison to the general population.[47] However, there is data suggesting that the incidence is significantly lower than this, with HIV men twice as likely to develop seminoma but at a higher risk of nonseminomatous germ-cell tumors.[48] HIV patients have an increased risk of high-grade testicular lymphoma as well as contralateral tumors.[49] Except surveillance, all accepted treatments for testicular neoplasms cause additional immune suppression. Furthermore, there is a suggestion that patients with advanced HIV/AIDS tolerate radiotherapy and chemotherapy poorly.[50] Major modifications are required in the standard treatment protocols, resulting in decreased effectiveness. However, in the absence of evidence most experts would recommend standard treatment.[51]

SEXUAL DYSFUNCTION

As the life expectancy of patients with HIV increases, quality of life issues, including sexual problems, are gaining importance. Erectile dysfunction (ED), reduced sexual desire, and premature ejaculation are common in men with HIV infection.

The underlying etiology behind sexual dysfunction in patients with HIV is multifactorial and involves a complex interplay between psychological and physiological components. The diagnosis of HIV alone can have a profound psychological effect on the patient. Long periods of sexual abstinence, fear of HIV transmission, and obligatory use of a condom can contribute to a psychological fear of sex and consequently sexual dysfunction.[6] The use of HAART in the treatment of HIV is associated with changes in body shape, and metabolic as well as hormonal control, all of which contribute toward a degradation in the patient's sexual function, both psychologically and physiologically (Figure 1).[6] Many patients with HIV find that they perceive their body differently, partly as a consequence of lipodystrophy which occurs most commonly around the face due to ART.[52,53] This visible manifestation of their therapy can cause concern as some perceive it as progression and also worry that it may lead to unintentional disclosure of their diagnosis.[53] Depression can affect up to 22% of patients with HIV and might be even higher especially in those who are substance abusers.[54,55]

Hypogonadism

Hypogonadism is common in men with HIV infection and can manifest as sexual dysfunction, fatigue, and low mood.[56–58] Men

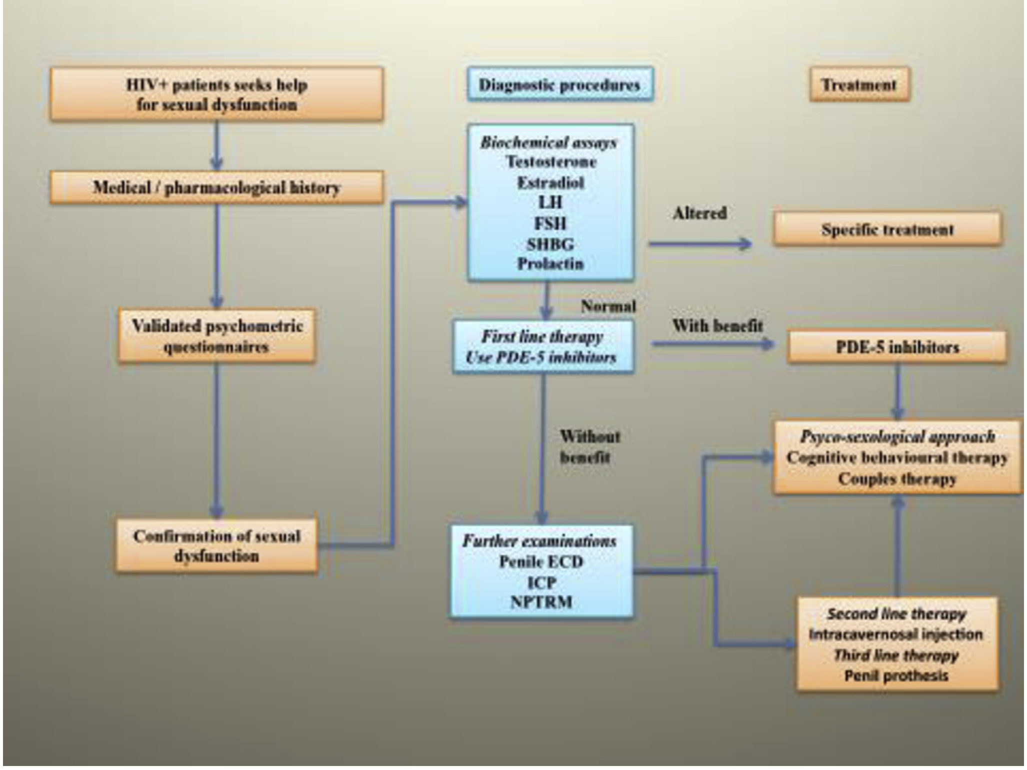

Figure 2. Diagnosis and therapeutic approach to ED in men with HIV. ECD = eco-color doppler; ICP = intracavernosal pharmacotherapy; NPTRM = nocturnal penile tumescence and rigidity monitoring; SHBG = sex hormone binding globulin.

with HIV infection appear to have an increased risk of hypogonadism compared to age-matched men without HIV. A clinical study reported that 30% of all HIV-positive men are hypogonadal.[59] Although testosterone replacement in hypogonadal men with HIV may have a positive effect on depression, it is also recognized in those patients without biochemical evidence of hypogonadism.[60]

Erectile Dysfunction

ED is more prevalent in men with HIV than in age-matched men without HIV.[61] The reported prevalence of ED among men with HIV varies widely from 9% to 74%.[62,63] In men with HIV the pathophysiology of ED is complex and rarely exclusively limited to only one of the following causes: neurological, vascular, endocrinologic, psychiatric, psychosocial disorders, and pharmacological.[64] The list of factors contributing to ED in men with HIV is given Table 2.

Both HIV infection and antiretroviral drugs can lead to ED. There appears to be evidence that the type of therapy used can have an impact on the patient's ED. Patients who are started on protease inhibiting (PI) drugs are 3.4 times more likely to complain of ED, which has been observed to resolve or reduce once omitted or substituted.[65,66] A large study of patients with HIV across 10 European countries revealed that ED and a reduction in sexual interest (both men and women) were more common in patients on PIs than PI-naïve patients.[67] Indinavir and ritonavir are the antiretroviral drugs most commonly associated with ED.[67–69] Atazanavir, a new PI whose metabolic pathway is different from that of others, showed an "unexpected" improvement of sexual function.[70]

As in the general population, the first step in evaluating sexual dysfunction in patients with HIV is always a detailed medical history to identify the underlying causes and risk factors. A detailed list of medications as well as an assessment of the patient's general health status including smoking and alcohol history is mandatory.[71] A thorough examination should be performed including assessment of androgenization, abdomen, genitals, and neurovascular status. The patient should have his waist circumference, blood pressure, and BMI recorded. The degree of ED should ideally be quantified using a validated questionnaire.[72] The International Index of Erectile Function (IIEF) is the most widely used tool; however, it is not validated in MSM.[73] However, the IIEF has been adapted and a separate questionnaire validated for this group of patients.[74] The patient should have serum sent for analysis to identify any metabolic and endocrine diseases, including hypogonadism, dyslipidemia, and diabetes mellitus.

Treatment of Sexual Dysfunction

Patients should be counseled regarding the impact of identified modifiable lifestyle choices (ie, smoking, drug abuse, alcohol abuse, obesity, and sedentary lifestyle). With close liaison with the patient's HIV team, and taking into account the viral load and CD4 count, the PI should be substituted where it is felt to be contributing to the ED.

PDE-5 inhibitors are the most common first-line medical treatment in all patients with ED. Although there have been concerns in the literature that their use in HIV patients promotes transmission, this should not prejudice treatment as long as patients are counseled robustly regarding the importance of practicing safe sex.[75]

When prescribing for patients with HIV on PI and HAART, it is important to take into account that the bioavailability of the PDE-5 will be increased and accordingly a dose adjustment should be made to reduce the risk of adverse events.[76–78]

In patients where a PDE-5i fails to restore normal erections, second-line therapies can be introduced, including intracavernosal injection or the transurethral application of prostaglandin E1.[71,72] However, intracavernosal injection can lead to the extravasation of blood and therefore increase the risk of transmission.[6] Third- and fourth-line options include vacuum pump devices and penile prostheses, both malleable and inflatable (Figure 2).[71]

In patients who are deemed hypogonadal, testosterone replacement can be employed to help restore normal sexual desire and work synergistically with PDE-5 to improve erectile function.[79]

CONCLUSION

As a result of advancements in pharmaceuticals, life expectancy of men infected with HIV has improved almost to that of the general population in developed countries. Therefore, clinicians are dealing with non—life-threatening urological problems that affect the quality of life of men with HIV. The majority of these problems can be managed easily, by adapting a "patient-centered" approach, instead of "disease-centred" algorithms.

Corresponding Author: Ege Can Serefoglu, MD, FECSM, Bagcilar Training & Research Hospital, Department of Urology, Istanbul, Turkey. Tel: +90 533 369 8222; Fax: +90 212 440 4010; E-mail: egecanserefoglu@hotmail.com

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STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Ege Can Serefoglu, MD, FECSM
(b) Acquisition of Data
Haci Ibrahim Cimen, MD
(c) Analysis and Interpretation of Data
Arie Stewart Parnham, MBChB, FRCS (Urol)

Category 2

(a) Drafting the Article
Haci Ibrahim Cimen
Arie Stewart Parnham
(b) Revising It for Intellectual Content
Ege Can Serefoglu

Category 3

(a) Final Approval of the Completed Article
Ege Can Serefoglu

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