

29. Sexual Dysfunction in HIV/AIDS

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Introduction

The “Multinational Survey of Aging Males” (MSAM), an international study of 14,254 men aged 40 to 70 years, showed a continuous vital interest in sexual activity in that age group: 83 % classified their sexual desire and interest as an important or very important component of their life and the average frequency of sexual activity was 5.8x /month. From other studies it is known that erectile dysfunction has a serious impact on the quality of life for men (Feldman 1994).

Many factors affect sexual function and sexual experience, with a key role being age (Feldman 1994). HIV infection can lead to sexual dysfunction because of the well-known interactions of the reproductive system with the immune system, the endocrine and the neuroendocrine systems. HIV infection has a significant psychological impact, and furthermore long-term antiretroviral therapy might have a negative psychological effect on the sexual experience. In patients on HAART, features of the lipodystrophy syndrome resemble the characteristics of the classic metabolic syndrome with raised insulin resistance, excess weight (abdominal girth > 102 cm), dyslipidemia and hypertension (> 130/85 mmHg). The clear association between metabolic syndrome and erectile dysfunction (ED) makes ED a predictive marker of the metabolic syndrome (Shabsigh in 2005).

The data relevant to sexual dysfunction in HIV patients is discussed in the following pages, with the acknowledgment that many questions remain regarding its causes and treatment.

Definitions

Erectile dysfunction or Impotentia coeundi is defined as the “constant or repeated appearance of an inability to attain or maintain an erection which is sufficient for the satisfactory execution of sexual intercourse,” (NIH 1993). The diagnosis is made if the problem has existed for a minimum of 6 months, and if at least 70 % of attempts to carry out sexual intercourse have been unsuccessful.

It is important to clearly separate ED from libido disturbance, defined as a decreased or entirely absent sexual drive or desire, and ejaculation disturbance, clinically apparent most frequently as Ejaculatio praecox or Ejaculatio tarda.

Etiology of sexual dysfunction in HIV/AIDS

The causes of sexual dysfunction (SD) are plentiful. A paradigm shift has taken place since 1980: improved diagnostic tests and better knowledge of the aging processes in men have led to the belief that 80 % of the cases have some organic involvement and 50 % of cases are exclusively organic in nature. A monopsychological cause is responsible for only 20 % of the cases (NIH in 1993). In HIV a “disease-specific” peculiarity lies in the fact that the probability of an SD is

not only increased by the chronic illness but by the comorbidities that are associated with HIV and the aging patient population, the psychosocial stress factors and the need for polypharmacy (Crum 2005).

Age

The most important biological cause of ED is age. ED exists in variable degrees, from light (17 %) to moderate (17-34 %) to complete (5-15 %) in 52 % of all men aged 40 to 70 years (Feldman 1994). The overall prevalence of ED ranges from 7 % in men aged 18-29 years (Laumann 1999) to 85 % in men aged 76-85 years.

Both the increased lifespan and the higher quality of life have a growing influence on the incidence of SD in HIV patients. Furthermore, biological changes, such as the declining testosterone production, decreasing sensitivity of the erectile tissues secondary to the decreasing neural or hormonal stimuli, and circulatory problems occurring with age, are further boosted in the context of HIV infection and HIV therapy.

Risk factors: diseases and comorbidities

Important ED risk factors coexist frequently in HIV patients, including excessive alcohol consumption, smoking and other recreational drug use; metabolic disorders (hyperlipidemia, diabetes mellitus); and cardiovascular disease, with hypertension being of particular importance. Pathophysiologically, most cases of ED are caused by neuronal (polyneuropathy) and vascular (micro- and macroangiopathy) changes; however, ED can also be an early sign of a metabolic syndrome.

Other possible risk factors are endocrine disorders, various neurological illnesses (i.e. disc prolapse) and infectious diseases. A frequent cause of ED in young men is chronic kidney or liver dysfunction (hepatitis, cirrhosis). Psychosocial problems, relationship conflicts and psychiatric illnesses (e.g., depression) are frequently related to sexual dysfunction. As a consequence, HIV patients have an increased risk for erectile dysfunction.

Table 1: Substances/Substance classes which may cause Erectile Dysfunction

Alcohol	Nicotine
Antihypertensives	Antidepressants
Diuretics	Antirheumatics (NSAR)
Lipid lowering agents	H2-Antagonists, proton pump inhibitors
Anticonvulsants	Tranquilizers
Opiates	Gestagens/estrogens
Chemotherapeutics, HAART	Amphetamines, hallucinogens

Medication

Many drugs have a negative influence on sexual function, predominantly on the libido and the ability to gain an erection. See Table 1 for an overview of the relevant substance classes in this context. Antiretroviral medications are also associated with SD; and both the duration and the combination of therapies have an accelerat-

ing effect. In a standardized survey on 78 HIV-infected men who have sex with men (MSM), conducted by Cove in London in 2004, 69 % reported at least one sexual partial dysfunction and 38 % indicated ED. All antiretroviral drugs can decrease sexual function. Some studies (Colson 2002, Schrooten 2001, Martinez 1999) showed PIs to be the main culprit, however, at least one study found no effects of specific drug classes (Lallemant 2002). Our own observations suggest that combinations of NRTIs and PIs work synergistically.

Ongoing research

An increasing prevalence of SD of up to 50 % was seen in HIV-infected men during the early 1990s (Meyer-Bahlber 1991, Catalan 1992, Tindall 1994). Similar results were observed in HIV-infected women (Brown 1993, Pergami 1993, Goggin 1998). In a prospective study (Lamba 2004) a clear increase in the prevalence of libido loss (48 %) and ED (25 %) was seen in HIV positive MSM on HAART, compared to HIV positive MSM not on antiretroviral therapy (26 % both) or HIV negative MSM (2 and 10 % respectively).

A survey of 904 HIV-infected men and women in 10 European countries (Schrooten 2001) showed that libido loss and ED existed significantly more frequently in patients on therapy containing a PI compared to patients naïve to PIs (40 vs. 16 % for LL and 34 vs. 12 % for ED, respectively). In a multivariate analysis, the following factors were identified for libido loss: current or previous use of a PI, symptomatic HIV infection, age, and MSM. Additionally, taking tranquilizers was found to be an independent risk factor for ED.

The impact of PIs in SD was also seen by Collazos (2002) in a prospective study of 189 patients. No correlation could be found between measured sex hormone levels and incidence of SD. Interestingly, in subjects taking a PI-containing regimen, testosterone levels were significantly higher compared to NNRTI-containing regimens in which 17 β -estradiol levels were significantly elevated.

In a standardized questionnaire of 156 MSM, no role for PIs as the cause of SD could be ascertained (Lallemant 2002). 71 % of the participants indicated signs of SD since initiation of ART; however, in therapy stratified groups (PI: 71 %, without PI: 65 %, no PI in the last 4 weeks: 74 %) there were no significant differences seen between patients taking or not taking a PI. 18 % of the participants had already suffered from SD before the diagnosis of HIV infection, and 33 % before the initiation of ART. The impact of psychological factors is highlighted by one study, in which the rate of HIV-positive MSM with ED rose from 38 to 51 % with the use of condoms (Cove in 2004).

More recent research impressively underscores the positive effect of testosterone substitution in HIV-infected hypogonadotropic men (Rabkin 2000, Grinspoon 1998). Testosterone deficiency can cause weight loss, loss of muscle mass, osteopenia, and depression (Grinspoon 1996, Huang 2001, Rietschel 2000).

Diagnosis of sexual dysfunction

A diagnostic work-up for the causes of SD is required before therapy. This includes a complete anamnesis with emphasis on sexual, social and family history and

should include potential social (recreational drug use) and familiar risk factors (i.e. diabetes mellitus), as well as a complete medication history. A thorough physical examination is obligatory. A diagnostic test of the morning blood level of testosterone is of central importance to determine the testicular endocrine function. The calculated index of free testosterone is the recommended parameter to follow, since this index reflects the real biological activity of testosterone. The direct determination of free testosterone by the lab has been identified as being unreliable (www.issam.ch).

Table 2: Laboratory diagnostics for erectile dysfunction

Special hormone diagnostics	General work-up
Testosterone (free circulating testosterone)	Cbc
Luteotropic hormone	Glucose, HbA1c
Follicular stimulating hormone	Lipid panel
Poss. LHRH	
Poss. HCG	possible: TSH
Poss. prolactin, PSA	Urine analysis

Low testosterone level requires determination of LH and FSH. Further work-up may require a LH or FSH stimulating test, usually handled by an endocrinologist, to exclude secondary hypogonadism. NPT (nocturnal penile tumescence measurement) is considered as minimally invasive and measures nocturnal erections. 3-6 erections per night of at least 70 % rigidity, lasting 10 minutes, are considered normal values. The question of morning erections can serve as critical criterion for the sexual anamnesis.

Further andrological diagnostics include sonography of the scrotum and, if the mammary glands are enlarged or involvement of the hypophysis is suspected (i.e. by an increased prolactin or estrogen level), an MRI of the Sella turcica is indicated. Other diagnostic tests used for the vascular work-up include Doppler sonography of the penis and pharmacocavernosography; and for the neuro-physiological work-up a Cavernosum EMG, vibrometry, sphincter- and N. pudendus-EMG. These are rarely necessary and left to the urologist.

Therapy for sexual dysfunction

General overview

Phosphodiesterase 5 inhibitors (PDE-5 inhibitors: sildenafil, vardenafil, tadalafil) have substantially improved the therapy of ED. They are simple to take, effective and, in general, relatively well tolerated. However, with the exception of a few private insurance companies, PDE-5 inhibitors are not covered by insurance plans, and so must be paid for by the patients themselves. With the introduction of PDE-5 inhibitors, intra-cavernous erectile tissue injection or the intra-urethral application of vasoactive prostaglandins has clearly receded into the background. Today, surgical interventions, such as penile vein surgery, revascularization surgery or prosthodontics, also no longer play a role.

For the HIV physician, it is important to know the interactions between PDE-5 inhibitors and HAART (particularly protease inhibitors and the NNRTI delavirdine). Through an inhibition of the cytochrome p450 enzyme system (CYP3A4) the level of PDE-5 inhibitors in the plasma is increased. This needs to be discussed with the patient. In particular, for patients using a boosted PI regimen PDE-5 inhibitors need to be started at a low dose. We specifically recommend a mini test dose at the beginning (e.g., 1/4 of a tablet of sildenafil 50 mg) and increase according to the success and side effects. Our experience indicates that a significant proportion of patients have the desired success with such a low dose. However, some patients do not achieve any effect with these low dosages (HIV infection of several years, multimorbidity, and psychological overlap). In these patients, the approved maximum dose should not be exceeded. Simultaneous administration of nitrate containing medications or substances containing nitrites ("poppers") is contraindicated since it may cause therapy-resistant hypotension.

Sexual activity is physically tiring and can be a strain on the cardiovascular system. If it is not clear whether a patient has an underlying cardiovascular problem, it is advised to screen for it before prescribing ED drugs. This is particular true if unstable angina is suspected.

Apomorphine is a centrally effective dopamine receptor agonist. It is less effective and so is less important in the treatment of ED, but should be considered in patients with contraindications to PDE-5 inhibitors (APO-go ampullae, max. 100 mg s.c.). Apomorphine seems to be particularly helpful in psychogenic ED and light organic ED. Miscellaneous herbal substances (Yohimbine, Maca, *Turnera diffusa*) might have a positive effect on sexual function. However, systematic studies have not been performed. These substances have little side effects, however, monitoring, especially for possible interactions with HAART, is advisable. For psychosocial problems, relationship conflicts or depressive disorders, psychotherapeutic support and if necessary a sexual-medical discussion are advised.

PDE-5 inhibitors

Sildenafil (Viagra™)

Sildenafil was licensed in the USA in 1998, and shortly afterwards in Europe, as the first PDE-5 inhibitor. Sildenafil is available in dosages of 25, 50 and 100 mg. The first effects are seen between 12 and 40 mins (mean 25 mins) after taking the medication. This can be delayed if a fatty meal or alcohol is consumed simultaneously. The maximum plasma concentration is reached after approx. one hour, the clinical time of effectivity lies within approx. 8 – 12 hours.

The response rate is dependent on the etiology of ED, but varies between 43 and 83 %. The most frequent side effects seen are headaches (11 %), flushes (11 %), dyspepsia (3 %), dizziness (3 %), rhinitis (2 %) and color blindness (1 %).

Because of synergistic effects of PDE-5 inhibitors with nitrates and NO-donators (e.g. molsidomin) the simultaneous consumption of those two substance classes can lead to vasodilatation and therefore to severe hypotension. The combination is absolutely contraindicated. Clarification with the patient is needed, since the use of amyl nitrates ("poppers"), or similar substances used as sexual stimulants, is

prevalent in some of the groups more affected by the HIV epidemic (i.e. the gay scene).

Epidemiologic studies have so far not shown a statistically increased likelihood of angina pectoris, myocardial infarct or deaths under sildenafil use.

Vardenafil (Levitra™)

Vardenafil was licensed in 2003. Phosphodiesterase 5 or the hydrolysis from cGMP is restrained approx. tenfold greater than by sildenafil, but the bioavailability, at 15 %, is low. Vardenafil is available in a dosage of 10 and 20 mg. First effects are seen approx. 15 to 30 mins after taking the medication; maximum plasma concentrations are reached after 60 mins. The clinical effect can last up to 12 hours.

Randomized, placebo-controlled studies, evaluating satisfaction with the amount of erection, showed a response rate of between 48 and 80 %. The response rate for successful sexual intercourse with ejaculation was approx. 75 %. Vardenafil is well tolerated by patients on antihypertensive therapy and is effective in these patients.

The same contraindication for the combination with nitrates and NO-donators exists. Adverse events include – as with sildenafil – headache (10-21 %), erythema (5-13 %), dyspepsia (1-6 %) and rhinitis (9-17 %).

Tadalafil (Cialis™)

Tadalafil was licensed in 2003. Dosages of 10 and 20 mg are available. Compared to other PDE-5 inhibitors the maximum plasma concentration is reached at 2 hours, the first effect is noticeable after 15 to 20 minutes. Since the plasma half-life is approx. 17.5 hours, the medication is effective up to 36 hours after intake. Personal observations point to the fact that these circumstances promote the popularity of tadalafil in the gay scene (“weekend pill”).

Headache (7-21 %), dyspepsia and heartburn (1-17 %), myalgia (3-7 %), back pains (4-9 %), rhinitis (5 %) and flushes (1-5 %) are the most frequently observed side effects. Clinical influences on the cardiovascular system could not be observed; an increased incidence of myocardial infarction was not seen in any study.

Recent studies with MSM suggest a connection between the intake of drugs, the intake of PDE-5 inhibitors and sexual risk behavior (Swearingen in 2005, Jackson in 2005).

Testosterone

Substitution therapy is clearly indicated for a documented lack of testosterone with clinical symptoms. Possible options are intramuscular injections (testosterone depot 250 mg i.m. with an interval of 14 to 21 days) or application in the form of a gel (e.g., testogel 25 mg/50 mg daily). Oral substitution is possible (e.g., andriol testocaps), but has not proved itself in clinical everyday life. The depot injection of 1,000 mg testosteroneundecanoat (Nebido™) has recently been recommended in intervals of 3 months with an increasing dose 6 weeks after the initial one. The advantages of the depot injection lie in the more even serum concentrations of testosterone. In times of limited recourses, it is advisable to document the testosterone deficit and the appropriate clinical symptoms precisely.

It has been pointed out that testosterone injections may promote growth of a carcinoma in situ of the prostate. A yearly PSA measurement appears to be advisable during therapy, as well as a baseline physical examination before starting substitution. However, this is not covered by health insurances. Moreover, with a positive family anamnesis, a urological consultation is advisable before the beginning of the substitution.

Hair loss, skin irritation (with the gel!), increase in serum liver enzymes, the lipid panel and the e-phoresis, as well as water retention in tissues, have been described as relevant side effects.

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