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Sexual dysfunction in the highly active antiretroviral therapy era

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Abstract

The possible relationship between HAART and the development of sexual disturbances of HIV-infected patients remains yet unresolved because of the inconsistency of the results of the different studies. To analyze the current knowledge on this topic, MEDLINE files were searched for articles dealing with any manifestation of sexual dysfunction in the HAART era. Selected references from these articles as well as communications to the main HIV meetings were also reviewed. Sexual dysfunction seems to be a very common event after the introduction of HAART. The average prevalences of sexual dysfunction among the different studies was 51%, erectile dysfunction 46%, decreased libido 44%, ejaculatory disturbances 39% and orgasmic disorders 27%. These disturbances seemed to be more common in patients treated with protease inhibitors. Several relevant questions related to sexual dysfunction in these patients are addressed in this review, including the possible pathogenic mechanisms involved. Despite the inconsistent results among the studies, the data that support a direct or indirect role of HAART in the generation of these disturbances seem to exceed the data that do not support it. As a conclusion, antiretroviral therapy, particularly protease inhibitors, seems to be to some extent directly or indirectly related to sexual dysfunction through different mechanisms.
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Key words

Sexual dysfunction. Highly active antiretroviral therapy. Protease inhibitors. Adverse effects. Erectile dysfunction.

Introduction

The introduction of highly active antiretroviral therapy (HAART) in the mid-1990s resulted in a dramatic benefit in the outcome of HIV-infection, but also in the appearance of many adverse events related to this therapy. Shortly after the generalization of HAART as the standard of care, a report suggested the possible association between protease inhibitors and the development of sexual dysfunction in 14 patients who had developed such a complication despite significant improvement in their clinical conditions[1]. Although sexual dysfunction was a common complication in HIV-infected patients before the HAART era, the disturbance was often related to advanced HIV disease and hypogonadism, both conditions frequently observed in these patients[2-6]. Therefore, the emergence of new-onset sexual dysfunction in patients who were otherwise asymptomatic and in good clinical condition was unexpected.

During the following years a few additional reports found, or failed to find, an association of HAART with these disturbances and, at present, the issue remains unresolved. However, it is remarkable the scarcity of studies specifically devoted to analyzing this problem, despite its high prevalence and the significant impact that these conditions may have on the patients' quality of life, both from a personal and social perspective[7], and even on the adherence to HAART[8]. This article summarizes the current knowledge on this topic and addresses several important questions regarding sexual dysfunction in the HAART era.

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Search strategy

The literature has been reviewed for published articles dealing with any form of sexual dysfunction in patients receiving HAART. MEDLINE files were examined since the introduction of HAART in 1995 to date, and references from the selected articles were also scrutinized. The search terms were sexual dysfunction, erectile, ejaculatory, libido, and orgasmic. Truncation was also used to retrieve articles that utilized related terms. Abstracts from the main HIV conferences, selected according to the same search strategy, have also been included in this review. However, they were dismissed if a paper from the same authors reporting essentially the same findings was published later in a journal.

How common is sexual dysfunction in the HAART era?

Studies conducted before the HAART era in patients with different risk factors for acquisition of the infection demonstrated that sexual dysfunction was more prevalent in HIV-infected than in their noninfected counterparts with the same risk factors[9,10]. However, the prevalence of sexual dysfunction is difficult to establish because the published studies differ greatly in design, setting, type of patients and symptoms evaluated and, in addition, the reporting of results is frequently inconsistent. Furthermore, the complexity of the diverse manifestations of sexual dysfunction and the lack of accurate instruments to evaluate many of them add further difficulties to the estimation of the true prevalence of the disorder.

Symptoms of sexual dysfunction include erectile dysfunction, loss of libido, premature or delayed ejaculation, orgasmic disturbances, priapism, and dyspareunia, among others[11]. However, the published studies have focused on different symptoms and the procedures of evaluation of them have also been different. Therefore, the comparison among studies may be difficult and discordant rates of sexual dysfunction are not unexpected.

Table 1 summarizes the frequency of diverse symptoms, as well as other descriptive parameters, in the studies carried out after the introduction of HAART. Considering the broad range of prevalences reported, the average values of different symptoms have been calculated from those series that provide specific data in order to obtain a more accurate estimation of the true prevalence of the diverse manifestations. According to this approach, the prevalence of erectile dysfunction would be about 46% (range 9-74%), decreased libido 44% (range 24-73%), ejaculatory disturbances 39% (range 36-42%), and orgasmic disorders 27% (range 7-49%). In those reports that do not describe specific symptoms or that analyzed sexual dysfunction in general, this disorder occurred in 51% of patients (range 6-90%), without substantial differences between men (59%, range 19-90%) and women (51%, range 25-84%).

Therefore, it seems clear that sexual dysfunction constitutes a very common event in these patients, especially taking into account the young age of the patients (average of the mean ages reported 38 years, range 30-41). These rates are considerably higher than those observed in the general population of similar age[7,30,31], although not much higher than that of patients studied before the HAART era[2-5,32,33]. However, it is important to consider that the clinical, virologic and immunologic conditions of the patients (average of the mean CD4 reported 445/µl, range 300-548) were substantially better than those observed in the studies conducted before the HAART era, and that the prevalence of hypogonadism and advanced HIV disease, which was responsible for a substantial part of the sexual dysfunctions in the past, has also been substantially reduced as a consequence of HAART[23,34,35].

Is HAART responsible for these disturbances?

The possible role of antiretroviral drugs in the generation of sexual dysfunction is controversial. Whereas some studies support the role of antiretroviral therapy[1,12-17,23,24,29,36,37], some others did not find such an association[18,21,22,25,26,28], discrepancies that can be attributed, among other factors, to the multiplicity of mechanisms involved, the diverse drug regimens used, the variety of symptoms evaluated, and the sample size and substantially different design of the studies.

Studies that do not support a role of HAART

A cross-sectional study on 82 women with a very high prevalence of two well-known predisposing factors to sexual dysfunction, such as depression and anxiety, briefly mentioned that HAART did not seem to have an influence on an array of psychosocial manifestations related to the sexual sphere[25]. However, these results cannot be analyzed because they were not described in the article and, on the contrary, it was also mentioned that some patients attributed to HAART their loss of libido. Another cross-sectional study on 166 women, who also had a high prevalence of psychological disorders, failed to find significant differences between antiretroviral treated and untreated women, although 28% of the former improved with the modification or suppression of HAART[22].

A prospective study involving 300 men did not find any relationship between erectile dysfunction and protease

Table 1. Sexual dysfunction in HIV-infected patients treated with HAART

Year (Ref)	Patients (n)	Gender	Geographic setting	HIV transmission categories	Mean or median age (years)	Mean or median CD4/µl	Undetectable viral load	Method of evaluation	HAART	Type of dysfunction	Reported frequency (%)
1999[12]	97	Men (79%) Women (21%)	Belgium	NS	NS	NS	NS	Questionnaire	Yes, PI (100%)	Decrease in sexual appetite (men) Decrease in sexual appetite (women) Erectile (men)	42 40 35
2000[13]	125	Men and women (% NS)	Italy	NS	NS	NS	NS	Questionnaire	Yes, PI Yes, no PI All	Modification of sexual habits (i/w) Modification of sexual habits (i/w) Modification of sexual habits (i/w)	45 45 45
2001[14]	334	Men	Italy	IDU (52%) Homosexual (22%) Heterosexual (22%)	36	431	75% (< 5000 copies/ml)	Questionnaire	Yes, PI Yes, no PI All	Erectile Erectile Erectile	10 7 9
2000[15]	904	Men (80%) Women (20%)	Europe, multinational	Homosexual (55%) Heterosexual (22%) IDU (6%) IDU or sexual (10%)	39	300-400	43%	Questionnaire	Yes, PI Yes, no PI All	Decrease in sexual interest Erectile Decrease in sexual interest Erectile Decrease in sexual interest Erectile	40 34 16 12 37 31
2002[16]	189	Men	Spain	IDU (75%)	37	451	64%	Interview, prospective	Yes No All	Erectile, decreased libido and/or ejaculatory disturbances Erectile, decreased libido and/or ejaculatory disturbances Erectile, decreased libido and/or ejaculatory disturbances	24 4 19
2002[17]	254	Men	USA	NS	37	NS	NS	Interview, retrospective	Yes, PI (100%)	Erectile, loss of libido	32
2002[18]	156	Men	France	Homo- or bisexual	41	415	NS	Questionnaire	Yes (100%)	Erectile Decrease or loss of libido Orgasmic perturbation Ejaculation perturbation Any	62 63 49 42 71
2002[19]	413	Men	UK	Homosexual	NS	NS	NS	Self-reported	Yes (% NS)	Sexual dysfunction Loss of libido Erectile Retarded ejaculation	90 73 54 36

HAART: highly active antiretroviral therapy; IDU: injection drug use; PI: protease inhibitors; NS: not specified; i/w: improvement or worsening.

(continue)

Table 1. Sexual dysfunction in HIV-infected patients treated with HAART (continued)

Year (Ref)	Patients (n)	Gender	Geographic setting	HIV transmission categories	Mean or median age (years)	Mean or median CD4/µl	Undetectable viral load	Method of evaluation	HAART	Type of dysfunction	Reported frequency (%)
2003[20]	596	Men (72%) Women (28%)	Italy	IDU (36%) Homosexual (24%)	37	548	NS	Questionnaire	Yes (100%)	Sexual dysfunction	6
2004[21]	78	Men	UK	Homosexual	30-40	300-400	49%	Questionnaire	Yes (78%)	Any Erectile Loss of interest in sex Orgasmic	69 38-51 41 19-31
2004[22]	166	Women	Europe, multinational	Heterosexual (62%) IDU (21%)	36	> 500	NS	Questionnaire	Yes (79%)	Diverse (moderate to severe)	25
2004[23]	73	Men	UK	Homosexual (88%)	39	NS	NS	Questionnaire	Yes	Low libido Erectile	48 25
									No	Low libido Erectile	26 26
									All	Low libido Erectile	40 25
2005[24]	65	Men	USA	NS	39	460	NS	Questionnaire	Yes (61%)	Erectile	26
2005[25]	82	Women	UK (75% black Africans)	NS	38	> 300	37%	Questionnaire	Yes (59%)	Diverse	60-84
2006[26]	118	Men	USA	Homosexual (52%) Heterosexual (29%) Bisexual (18%) IDU (7%)	41	417	NS	Questionnaire	Yes No All	Erectile Erectile Erectile	80 65 74
2006[27]	34	Women	UK (97% black Africans)	NS	NS	NS	NS	Interview, retrospective	Yes (% NS)	Diverse Lack of desire Lack of orgasm	56 33 7
2007[28]	300	Men	USA (multi ethnic)	NS	39	522	41%	Questionnaire	Yes (60%)	Erectile	61
2007[29]	668	Men	Europe, multinational	Homosexual (73%)	40	498	72% (< 1000 copies/ml)	Questionnaire	Yes (83%)	Erectile Low sexual desire	33 24

HAART: highly active antiretroviral therapy; IDU: injection drug use; PI: protease inhibitors; NS: not specified; i/w: improvement or worsening.

inhibitors or antiretroviral therapy in the multivariate analysis, despite the highly significant association observed with the duration of HAART and the duration of protease inhibitor use in the univariate analysis[28]. In this regard, the same authors had reported previously an association between erectile dysfunction and the duration of HAART in another study on a lower number of patients[24]. Another cross-sectional study on 78 homosexual men also failed to find significant differences, although its statistical power was low and many patients imputed their sexual dysfunctions to HAART[21]. Other authors, using also a cross-sectional design, did not find differences in the sexual functioning of 156 homosexual or bisexual men, depending on the treatment or not with protease inhibitors, although the results were somewhat better for the protease inhibitor-naive patients[18]. Finally, another cross-sectional study, also with low statistical power, failed to find significant differences in the rates of sexual dysfunction between antiretroviral treated and untreated patients[26]. However, in this study there were some differences between the two groups (81 vs. 65%, respectively) and the statistical comparison between them ($p = 0.06$) almost reached the significance level.

Studies that support a role of HAART

A retrospective study on 274 men found a significant increment in the incidence of sexual dysfunction after the onset of protease inhibitors[37], and another retrospective study on 254 protease inhibitor recipients also found an association between these drugs, particularly ritonavir, and sexual dysfunction[17]. Similarly, a cross-sectional study on 334 men failed to find any significant relationship between erectile dysfunction and protease inhibitors considered as a whole, but it found such a relationship with indinavir use[14]. Also, the largest study published on this topic evaluated by means of an anonymous questionnaire more than 900 men and women from 10 European countries[15]. The results revealed that the rates of erectile dysfunction and decreased sexual interest were higher in patients receiving protease inhibitors as compared with protease inhibitor-naive patients[15]. Another large, multinational study that evaluated 668 men by means of a questionnaire found that erectile dysfunction, but not sexual desire, was associated with duration of HAART, after adjusting for many variables[29]. In this study, no association was found with specific antiretroviral drugs.

In a communication to a meeting, some authors reported that erectile dysfunction was associated with the use of protease inhibitors and with the time of exposure to HAART in 65 men[24]. In another communication on 125 patients, other authors reported changes in the sexual habits, either as improvement or worsening, in almost half of patients after the onset of HAART, although protease inhibitors were not associated with these changes[13]. Data from another meeting revealed a worsening in the sexual function of men after the onset of HAART, and higher degrees of dysfunction in antiretroviral-experienced than in naive men, although these differences were not observed in women[36].

A prospective and small study on 73 men failed to find significant differences in the rates of erectile dysfunction in patients treated or not with HAART, but found such differences in the libido of patients[23]. Another prospective, larger study on 189 men who underwent 351 evaluations found significantly higher rates of sexual dysfunction in patients treated with HAART as compared with naive patients, and in those receiving protease inhibitors compared with patients who did not received such drugs[16]. Remarkably, sexual functioning improved in some patients when the protease inhibitors were discontinued. Finally, diverse studies that have carried out multivariate analyses found an independent association of protease inhibitors[15], antiretroviral therapy[16], and indinavir[14] with the development of diverse manifestations of sexual dysfunction.

Regarding specific antiretroviral drugs, protease inhibitors in general[1,12,15-17,24,37], and indinavir[13-16] and ritonavir[15,17] in particular, have been the most commonly involved agents. However, most of the published studies were carried out with the earlier protease inhibitors. Therefore, the effect of the more recent members of the family is unknown at present. In this regard, anecdotal experiences suggest a sparing effect of atazanavir on the sexual function[38].

Therefore, causal role, or not?

Despite the discordant findings, the data that support a causal effect of antiretroviral drugs on these disturbances, either direct or indirect, seem to exceed the data that do not support such an effect. Interestingly, women seem to be over-represented in studies that did not find differences as compared with those that found them, which could indicate different effects according to gender. However, it should be considered that the symptoms evaluated in these studies were frequently different in men and women, as exemplified by erectile dysfunction that was the most studied manifestation of sexual dysfunction in men. Additionally, the high prevalence of psychological disorders (a well-known risk factor for sexual dysfunction) in two studies on women that failed to find differences in sexual functioning according to HAART[22,25] could have masked a certain role of antiretroviral therapy.

On the other hand, there has been reported improved sexual satisfaction in patients treated with nonnucleoside reverse transcriptase inhibitors[39], significantly less dys-

functional effect of nevirapine than protease inhibitors[40], and improvement in the sexual performance after discontinuation or change from protease inhibitors to other drugs[16,29,41]. Finally, the fact that the frequency of sexual dysfunction has not decreased in the HAART era with respect to earlier periods despite the significant improvement in the two main factors responsible for such disturbances, i.e. hypogonadism and advanced HIV-disease, supports the role of HAART in the generation of these disturbances.

Which are the possible mechanisms involved?

There is a multiplicity of factors (psychological, structural, neurological, pharmacological, biochemical and hormonal) involved in the sexual dysfunctions of the general population[7,30,31,42-45], which also apply to the HIV-infected individuals. In addition, certain factors characteristic of the HIV infection or its treatment may influence the absolute or relative impact of some of them. Finally, the common occurrence of mixed etiologies in the same patient adds further complexity and complicates the correct identification and classification of the causes.

Psychogenic factors

It is difficult to establish their exact role in the generation of sexual dysfunction. These factors have been invoked as responsible for many sexual disturbances in the general population[42,43], and seem to be particularly common among women attending sexually transmitted disease clinics[46]. Therefore, it is reasonable to assume that many of the sexual dysfunctions reported by HIV-infected patients are caused by these factors, the most relevant of them being anxiety, depression, and posttraumatic stress disorder. In fact a meta-analysis revealed that the prevalence of major depression was almost twice in HIV-infected patients than in seronegative individuals[47].

Specific social, ethnic, or anthropological factors, such as rape particularly in women from Africa, should also be considered significant factors in the generation of such dysfunctions in the appropriate settings. In addition, the psychological effects of HIV infection and its social, epidemiological, and clinical connotations add further complexity to the problem. Also, antiretroviral regimens, particularly those including the earlier protease inhibitors, are complex and troublesome and may also have psychological implications. In fact, sexual dysfunction was associated with nonadherence in patients receiving protease inhibitors, but not in those receiving nonnucleoside reverse transcriptase inhibitors in a study[8]. Therefore, psychogenic causes seem to be responsible for, or contributory to, a number of sexual dysfunctions in men[17,21,29,48,49] and women[22,49] infected with HIV.

In this regard, a study found that psychological factors alone, or in association with HIV disease itself and/or HAART, were the most frequently cited causes of sexual disorders according to the patients' own estimation[21]. In fact, primarily psychogenic sexual dysfunction was thought to be present in 44%, and mixed psychogenic and organic dysfunction in an additional 34%, of homosexual or bisexual HIV-infected men[48]. Remarkably, homosexual HIV-infected men seem to be especially prone to sexual dysfunction, with rates as high as 69%[21] and 90%[19]. In addition, homosexual HIV transmission proved to be an independent risk factor for sexual dysfunction in some[14,15] but not all[29] studies. However, a possible bias owing to higher rates of perception or reporting of these disturbances among this population cannot be dismissed.

Hormonal factors

Once common[2-6,32,50], the prevalence of severe hypogonadism, a well-known cause of sexual dysfunction[51-54], has now been markedly reduced[23,35], particularly in patients on HAART in good clinical condition who may have even higher testosterone levels than naive patients[34]. In fact, significant increases in testosterone and other steroidal hormones have been found in patients who initiated HAART as compared with their own pre-HAART values[23,34,55].

Of particular interest is that about one-half of men on HAART have increased serum levels of estradiol[23,34]. The cause of such a common disturbance may be related to an interaction of antiretroviral therapy with the metabolic pathways of estradiol, as well as to other factors such as alcoholic or viral liver disease or an enhanced activity of aromatase in the adipose tissue of lipodystrophy patients, resulting in an increased transformation of androgens to estrogens[56-58].

However, the role of estrogens in the erectile dysfunction is not clear. Whereas some experimental studies suggest that estrogens may affect the erectile function at the receptor level[59,60], the usual effect of estrogen excess is thought to be the inhibition of hypophyseal gonadotropin and subsequent decrease in the synthesis of testosterone[57,60,61]. Nevertheless, this mechanism does not seem to be responsible for the sexual dysfunction of these patients because some studies did not find depressed levels of gonadotropin in HAART-treated patients[34], or differences in the levels of gonadotropin, testosterone, or estradiol, depending on the presence or absence of sexual dysfunction[16]. In addition, patients whose sexual performance improved during follow-up in a study maintained increased levels of estradiol despite the improvement[16].

Another hormone that may be involved is prolactin, which may also cause sexual dysfunction through the inhibition of the hypothalamic factors and subsequent inhibition of the synthesis of gonadotropin[44,45,62]. Elevated serum levels of prolactin are also common in HIV-infected patients on HAART, involving about one-fifth of them[63], although macroprolactin, an isoform of low biological activity, seems to account for a substantial part of this elevation[64]. However, hyperprolactinemia does not appear to be responsible for the sexual dysfunction of most of these patients because no such inhibition of gonadotropin has been found[34], and patients with sexual dysfunction did not have higher prolactin values than those who did not complain of sexual disturbances[16].

Medications

Many drugs have been related to sexual dysfunction, some of them commonly used for the management of the comorbidity and complications associated with the HIV-infection or its treatment, such as megestrol, ketoconazole, antihypertensives, diuretics, benzodiazepines, antidepressants, antipsychotics, and opioids, either prescribed or illicit[29,31,44,45,65]. In addition, statins and other hypolipemic drugs, frequently used for the treatment of HAART-induced hyperlipemia, have also been related to sexual dysfunction in the general population[66], although these findings were not confirmed in patients infected with HIV in two studies[26,29].

Finally, it could be hypothesized that there is a direct effect of antiretroviral drugs on the androgen receptors, which could account for a hormonal mechanism of sexual dysfunction despite normal serum levels of testosterone. In this regard, some studies have found interactions of certain HIV protease inhibitors such as nelfinavir[67], or other protease inhibitors not related to HIV[68,69], with the receptors of steroid hormones.

Other mechanisms

There are many other conditions associated with sexual dysfunction, such as neuropathy, liver disease, hyperlipidemia, diabetes, vascular disease, hypertension, hepatitis C virus coinfection, tobacco, and alcohol consumption[31,43,44,59,70], which should be searched for because they are commonly found in HIV infection. In this regard, it should be remembered that patients infected with HIV under antiretroviral treatment may be at risk for development of different types of neuropathy that could be responsible for the sexual dysfunction of some patients[14,35,71-73].

How should these patients be evaluated?

It is beyond the scope of this review to provide detailed diagnostic approaches or management strategies for these disturbances. In general, the evaluation of HIV-infected patients does not differ from that of the general population, although special attention should be paid to certain aspects related to HIV infection and its treatment, including the psychological issues. The first step should be the detection of patients with these disorders, which is often overlooked in clinical practice because many patients are reluctant to discuss these symptoms and doctors commonly do not ask about them. To this end, there are standardized and validated questionnaires on sexual performance and satisfaction, which may help to obtain a more accurate estimation of the presence and severity of symptoms of sexual dysfunction in men and women[74,75]. A focused history and physical examination of patients are mandatory, paying special attention to the existence of comorbid processes associated with sexual dysfunction and to the presence or absence of nocturnal erections, which may suggest a primarily psychological or organic cause, respectively. A drug history is also essential because certain drugs, either antiretrovirals or not, seem to be associated with increased prevalence of sexual dysfunction, and patients may even be able to identify the drugs possibly related to the disorder.

Initial laboratory evaluation should include a lipid and metabolic profile and, if feasible, serum free or bioavailable testosterone, rather than total testosterone because HIV-infected patients may have increased levels of sex hormone-binding globulin[2,32]. In patients with low testosterone levels, gonadotropin and prolactin should also be measured in order to verify the origin of the hypogonadism. Determination of serum estradiol could also be considered, despite its role in sexual dysfunction not being clear, because interventions to reduce estradiol levels may be undertaken in certain patients with substantially elevated values of estrogens[76]. More complicated and specialized studies, such as urologic and neuropathic investigations, should be reserved for selected patients in whom an organic cause is suspected but remains undiagnosed despite the initial studies.

How should sexual dysfunction in the HIV-infected patient be managed?

As in the diagnostic evaluation, the general management strategies for HIV-infected people with sexual dysfunction are analogous to those of noninfected individuals. Psychosexual or cognitive therapy is initially indicated for patients in whom a psychogenic cause is suspected, including the proper use of antidepressants or other psychotropic drugs

if needed. For those with an organic origin, treatment of the cause, if identified and feasible, would be indicated. Hypogonadism should be treated with testosterone because hormonal replacement therapy may solve the sexual disturbance and has additional beneficial physical and psychological effects in hypogonadal patients. However, androgens are not recommended for patients with normal levels of testosterone because no significant benefit in terms of sexual function is expected in non-hypogonadal patients and, in addition, they may be associated with significant adverse effects. On the other hand, correction of the elevated levels of estradiol seen in about one-half of patients receiving HAART will probably not result in an improvement of erectile dysfunction in most patients, according to the very scanty information available. In fact, protease inhibitors, which seem to display a favorable profile regarding the balance testosterone/estradiol[34] seem also to be the drugs most commonly involved in sexual dysfunction[1,12,15-17,24,37] and, in addition, nevirapine seems to be associated with a lower incidence of sexual dysfunction, despite the relatively unfavorable testosterone/estradiol ratio[40]. However, some improvement in sexual desire has been reported in a few patients on HAART who were treated with letrozole, an aromatase inhibitor that inhibits the conversion of testosterone to estradiol[76].

A number of drugs have been developed for symptomatic treatment of erectile dysfunction, but the most commonly used at present are the phosphodiesterase 5 inhibitors, sildenafil, vardenafil, and tadalafil. It should be underscored, however, that these drugs have significant interactions with protease inhibitors because both are metabolized by the cytochrome P-450 system. Concurrent administration of protease inhibitors and phosphodiesterase 5 inhibitors results in substantial increments in the concentrations of the latter and the need for appropriate dose adjustment[77-79]. In addition, concerns have been raised regarding potential changes in sexual behavior and lifestyle factors related to the use of these drugs[79]. Finally, intracorporeal injections and a variety of devices and surgically implanted prostheses are also available, although they are usually reserved for those patients who have not responded or did not tolerate pharmacological therapy.

In the particular case of HIV infection, special attention should be paid to psychological issues, such as depression and anxiety, so frequent in these patients, and to the non-antiretroviral drugs that they could receive. Regarding HAART, it seems reasonable to modify the antiretroviral regimen if a temporal relationship can be established between the incorporation of new drugs and the development of symptoms. Similarly, some drugs seem to display a more favorable profile regarding sexual function, such as nevirapine[40,41] and, according to anecdotal reports, atazanavir[38]. Therefore, modification of the antiretroviral regimen could contribute to improve or solve the problem in some patients[16,29,38,41], although the experience supporting this approach is limited.

Finally, as a conclusion of this overview, several of the questions expressed above remain open, although some progress has been made in the past few years. Considering the high prevalence of these disorders and their effects on the quality of life, further studies focused on this topic are mandatory to elucidate the mechanisms involved and the implication or not of specific antiretroviral drugs, particularly the new protease inhibitors.

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