Risk factors for sexual and erectile dysfunction in HIV-infected men: the role of protease inhibitors

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Objectives: To determine the prevalence of erectile dysfunction in a cohort of HIV-infected men in a stable clinical state, the effect of exposure to antiretroviral therapy on sexual dysfunction and to identify the risk factors.

Design: This is a cross-sectional, observational study.

Methods: HIV-infected men without hepatitis C virus coinfection were included if they were antiretroviral therapy-naive (naive group), on current treatment with an enhanced protease inhibitor (protease inhibitor group) or on current treatment with two to three nucleoside reverse transcriptase inhibitors along with one nonnucleoside reverse transcriptase inhibitor and never having received treatment with protease inhibitor (nonnucleoside reverse transcriptase inhibitor group). Erectile dysfunction was defined as an ejection fraction of 25 or less (International Index of Erectile Function-15).

Results: Ninety patients were included, with an age of 42 ± 8.2 years and $CD4^+$ cell count of 465 cells/μl [P_{25-75} 361–676]: 18.9% in Centers for Disease Control and Prevention class C and 72.2% with undetectable viral load. Seventy-six patients (84.4%) were receiving antiretroviral therapy, 39 (43.3%) in the protease inhibitor group. The prevalence of lipodystrophy was 31.5%. Forty-seven (53.4%) patients had an erectile dysfunction. Multivariate logistic regression analysis confirmed that there was an independent association between the patients' age (per decade; odds ratio 2.2, 95% confidence interval 1.04–4.5, $P = 0.04$) and greater duration of exposure to protease inhibitor (per year; odds ratio 1.6, 95% confidence interval 1.12–2.4, $P = 0.01$). Older age, depression and lipodystrophy, combined with the duration of exposure to protease inhibitor, determined a lower score on various sexual dysfunction domains ($P < 0.05$).

Conclusion: There is a high prevalence of erectile dysfunction in HIV-infected men, with age and the duration of exposure to protease inhibitor being the only identifiable risk factors.

AIDS 2010, **24**:255–264

Keywords: antiretroviral therapy, erectile dysfunction, HIV, prevalence, risk factors, sexual dysfunction

Introduction

Erectile dysfunction is defined as a persistent inability to achieve or maintain an erection adequate for satisfactory sexual intercourse [1]. Sexual dysfunction is a broader, more complex concept, which not only includes erectile dysfunction but also covers sexual desire, orgasms, satisfaction during intercourse and overall satisfaction [2].

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Received: 12 August 2009; revised: 11 October 2009; accepted: 15 October 2009.

DOI:10.1097/QAD.0b013e328334444b

ISSN 0269-9370 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins

The prevalence of erectile dysfunction in HIV-infected men is higher than in the general population [3,4]. The prevalence of erectile dysfunction determined using the International Index of Erectile Function (IIEF) questionnaire varies from 13 to 36% in men aged 40–49 years and from 25 to 43% in those aged 50–59 years [5,6]. Recent studies [7,8] in HIV-infected men aged 19–72 years found a prevalence of erectile dysfunction of 61–74% using the same questionnaire (IIEF).

The pathogeny of erectile dysfunction and sexual dysfunction in the HIV population is not clear, with risk factors present in the general population, such as age, and others specific to HIV infection, such as the stage of the disease, being involved. Just as in non-HIV-infected men, hormonal, vascular, psychological, neurological and cellular factors are involved [9]. Some studies [10–12] have found an association between antiretroviral therapy (ART), especially protease inhibitors, and sexual dysfunction due to mechanisms that are not well understood, although other studies [6,8,13] failed to find such an association. The role that ART plays in the development of erectile dysfunction is yet to be determined. Other factors not associated with ART, such as age, progression of HIV infection, $CD4^+$ lymphocyte count, depression and lipodystrophy, have been associated with sexual dysfunction [6,12–14]. Whether erectile dysfunction is linked to hypogonadism in HIV-infected men is not clearly settled [6,15,16].

The importance of erectile dysfunction lies not only in its impact on quality of life and psychosocial welfare, but it can also be an early sign of endothelial dysfunction, blood flow abnormalities and cardiovascular risk [17]. The objective of our study was to establish the prevalence of erectile dysfunction in a cohort of HIV-infected men in a stable clinical state and to look for associated factors including the effect of exposure to antiretrovirals.

Design and methods

A cross-sectional, observational study was carried out in the Infectious Diseases Unit of a tertiary hospital. The study was approved by the hospital's ethics committee for clinical research. HIV-infected men aged at least 18 years undergoing follow-up in the Unit were included if they were ART-naive or on the same ART for the previous 6 months. Only patients receiving two to three nucleoside reverse transcriptase inhibitors (NRTIs) along with an enhanced protease inhibitor (lopinavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir, saquinavir/ritonavir and tripanavir/ritonavir) or on two to three NRTIs along with a non-NRTI and who had never received treatment with a protease inhibitor were included. Patients were excluded if they were coinfected with hepatitis C virus, had any active AIDS-defining disease, diabetes mellitus, any use of prior androgen replacement therapy (either by prescription or self-use) or were receiving any treatment which may lower plasma testosterone levels (gancyclovir, ketoconazol, megestrol acetate, spironolactone, thiazide diuretics or steroids). Drug users (except for substitute treatment with methadone and cannabinoids), irregular follow-up, therapeutic noncompliance (impossibility of having accurate information about the history of exposure to different antiviral drugs), psychiatric illness or cognitive deficit, which make it impossible for the patient to understand the study, were also excluded. All the patients gave written consent.

Result variables

Erectile dysfunction

Each patient completed the IIEF-15 questionnaire by himself [18]. This questionnaire assesses erectile function, orgasmic function, intercourse satisfaction, sexual desire and overall satisfaction. For the purpose of the study, data collected on each domain were limited to the 4 weeks prior to the study. Erectile dysfunction was defined as an erectile function score of 25 or less [19]. Erectile dysfunction was classified into four diagnostic categories depending on the severity: no erectile dysfunction (erectile function score 26–30), mild erectile dysfunction (erectile function score 17–25), moderate erectile dysfunction (erectile function score 11–16) and severe erectile dysfunction (erectile function score 6–10).

Sexual dysfunction

With regard to the other sexual function domains, there are no validated diagnostic categories, and so, for the purpose of analysis, the scores obtained on all the domains evaluated by the IIEF-15 questionnaire were considered as quantitative variables. The lower the score on the various domains, the greater the sexual dysfunction.

Explanatory variables

Sociodemographic and lifestyle variables included smoking, alcohol consumption [quantified as low (<17 standard drink units, SDU/week), moderate (17–28 SDU/week) and high (>28 SDU/week)], cannabinoid consumption and physical activity. Variables related to HIV infection are risk practises, nadir and current $CD4^+$ lymphocyte count [cells/μl and percentage; flow cytometry, FASCalibur (Becton Dickinson Biosciences, San José, California, USA)], plasma viral load (copies RNA/ml, logarithmic units; lower detection limit 39 copies/ml; COBAS TaqMan HIV test; Roche Diagnostics, West Sussex, UK), duration of HIV infection in years and clinical state. Variables related to lipid and hydrocarbon metabolism are fasting glycemia and basal lipid profile, including total cholesterol (TC), low-density lipoprotein (LDL) cholesterol (LDLc), high-density lipoprotein (HDL) cholesterol (HDLc), and triglycerides. Variables related to hypogonadism are total testosterone measured between 0800 and 0900 h [chemoluminescent immunoassay, UniCell DXI 800; Beckman Coulter, Fullerton, California, USA (Access Testosterone; Beckman Coulter)]; hypogonadism was defined as a total testosterone level below the lower normal limit established by our laboratory (total

Table 1. Clinical characteristics of the whole cohort ($n = 90$).

	n (%)	Mean ± SD	Median (P_{25}–P_{75})
Age (years)	–	42.0 ± 8.2	–
CDC stage		–	–
A	53 (58.9)		
B	20 (22.2)		
C	17 (18.9)		
Duration of HIV (years)	–	7.8 ± 5.6	–
Nadir $CD4^+$ cell count (cells/μl)	–	–	205 (125–287)
Current $CD4^+$ cell count (cells/μl)	–	–	465 (365–676)
Viral load (RNA/ml)	–	–	39 (39–104)
Group		–	–
Naive	14 (15.5)		
NN	37 (41.1)		
PI	39 (43.3)		
Duration exposure (months)	–		–
Total ART		66 ± 42	
Non-NRTI		36 ± 27	
NRTI		111 ± 90	
PI		55 ± 40	
Current exposure to ART			
NRTI			
Tenofovir	38		
Azidothymidine	17		
Lamivudine	35		
Emtricitabine	25		
Didanosine	8		
Abacavir	15		
Stavudine	9		
Non-NRTI			
Efavirenz	34		
Nevirapine	3		
PI			
Lopinavir	23		
Atazanavir	10		
Fosamprenavir	3		
Tipranavir	3		
Alcohol consumption			–
No	51 (56.6)		
Yes	39 (43.3)		
SDU		8.6 ± 7.7	
Smoker		–	–
No	24 (26.7)		
Ex-smoker	7 (7.8)		
Yes	59 (65.6)		
Sedentary lifestyle		–	–
No	35 (42.7)		
Yes	47 (57.3)		
Beck depression		–	–
No	55 (61.8)		
Mild	24 (27.0)		
Moderate	6 (6.7)		
Severe	4 (4.5)		
AMS		–	–
No	33 (37.1)		
Yes	56 (62.9)		
ADAM		–	–
No	32 (36)		
Yes	57 (64)		
TT (ng/ml)		5.1 ± 1.4	
Hypogonadism TT <3 ng/ml	3 (3.3)	–	–
ED (IIEF-15)			
No	43 (46.6)		
Yes	47 (53.4)		
IIEF-15 domains			
EF			24 (14–29)
OF			9 (8–10)
IS			10 (6–13)
SD			7 (6–9)
OS			8 (6–9)
BMI (kg/m^2)	–	24.7 ± 3.4	–
WHR	–	0.95 ± 0.1	–

Table 1 (*continued*)

	n (%)	Mean ± SD	Median (P_{25}–P_{75})
Lipodystrophy		–	–
No	59 (67.9)		
Yes	28 (32.1)		
TC (mg/dl)	–	188.7 ± 42.2	–
LDL (mg/dl)	–	127.3 ± 40.5	–
HDL (mg/dl)	–	49.0 ± 14.3	–
TG (mg/dl)	–	–	174 (97–200)

Data are expressed in ng/ml × 3.467 nmol/l (TT), mg/dl × 0.0258 nmol/l (total, LDL and HDL cholesterol), and mg/dl × 0.01129 nmol/l (TG). NN, current ART with two to three NRTIs along with a non-NRTI and never received PIs; P_{25}–P_{75}, 25th–75th percentiles; PI, current ART with two to three NRTIs along with an enhanced PI. ADAM, Androgen Deficiency in Aging Men; AMS, Aging Male's Symptoms Scale; ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; ED, erectile dysfunction; EF, erectile function; HDL, high-density lipoprotein; IIEF-15, International Index of Erectile Function-15; IS, intercourse satisfaction; LDL, low-density lipoprotein; NRTI, nucleoside reverse transcriptase inhibitor; OF, orgasmic function; OS, overall satisfaction; PI, protease inhibitor; SD, sexual desire; SDU, standard drink units per week; TC, total cholesterol; TG, triglycerides; TT, total testosterone; WHR, waist–hip ratio.

testosterone <10.4 nmol/l; <3 ng/ml). Each patient also completed two questionnaires on hypogonadism symptoms (Androgen Deficiency in Aging Men, ADAM, and Aging Male's Symptoms Scale, AMS) [20,21].

Regarding somatometry, physical examination was carried out with determination of the BMI and waist–hip ratio (WHR). The presence of lipodystrophy was determined using a standard questionnaire for dystrophy based on physical examination. Patients with at least a moderate or a severe lipodystrophy (except isolated abdominal obesity), obvious both to the patient and to the two researchers evaluating the patient, were considered to have lipodystrophy [22].

Self-evaluation was done by filling out the Beck Depression Inventory: a score of at least 10 was defined as depression (mild 10–16, moderate 17–23 and severe >23) [23].

For the analysis of ART, the patients were classified into three groups: ART-naive (naive group), patients on ART with enhanced protease inhibitor (protease inhibitor group) and patients on a non-NRTI (non-NRTI group); non-NRTI group patients had never received treatment with protease inhibitor. Current medication, prior use of other ART and duration of exposures were recorded.

Statistical analysis

Qualitative variables were expressed as relative and absolute frequencies in percentages of each of the values of the variable. Parametric variables were expressed as means and SD, and nonparametric variables as medians and 25th and 75th percentiles. The prevalence of erectile dysfunction, with its 95% confidence interval (CI), was then calculated. Next, we studied whether there was an association between the clinical characteristics and erectile dysfunction, using the chi-squared test for qualitative variables and the Student's *t*-test or Mann–Whitney *U* test for quantitative variables. The odds ratio (OR) of prevalence was calculated with its 95% CI. A multivariate, unconditional, logistic regression analysis was then done in which all the variables with a statistical significance of *P* value less than 0.10 and those considered relevant were included as explanatory variables. The association between the clinical characteristics and each of the sexual function domains was studied using Spearman's correlation coefficient for quantitative variables, the Mann–Whitney *U* test for two categories of qualitative variables and the Kruskal–Wallis test for three categories of qualitative variables. For each of the sexual function domains, and using the variables that were found to be significantly associated in the bivariate analysis, a multivariate, multiple, linear regression analysis was done in which the coefficient of determination (r^2) was calculated for the whole equation. In all cases, a *P* value of less than 0.05 was considered statistically significant. The SPSS version 10.1 program (SPSS Inc., Chicago, Illinois, USA) was used.

Results

The study was offered to 109 men. Nineteen patients refused to give their consent; so finally, 90 patients were enrolled (Table 1).

The mean age of the patients was 42 years (range 25–68 years). All the participants were white. The patients' sexual orientation was 75.6% homosexual, 4.8% bisexual and 19.5% heterosexual. Only two patients had a $CD4^+$ cell count of less than 200 cells/μl. Sixty-six patients were receiving ART. The protease inhibitor group, when compared with the non-NRTI group, had a longer disease (10.1 ± 5.5 vs. 7.3 ± 5.2 years, $P = 0.026$), a longer time on ART (81.6 ± 46.7 vs. 50.4 ± 30.4 months, $P = 0.001$) and a longer time on the current ART [24 (16–43.5) vs. 16 (10–30) months, $P = 0.009$)]; there were no differences in age, nadir $CD4^+$ cell count, current $CD4^+$ cell count or viral load.

Twenty-eight patients (31.1%) answered yes to the direct question of whether they were impotent. Of these, eight

(28.6%) patients presented erectile dysfunction from HIV diagnosis, two (7.1%) developed erectile dysfunction less than 5 years after diagnosis despite being ART-naive, five (17.9%) developed erectile dysfunction after less than 5 years of ART and 10 (35.7%) developed erectile dysfunction after more than 5 years' exposure to ART. Impotence was progressive in 71.4% of patients, and 64% had spontaneous nocturnal erections.

Forty-seven (53.4%, 95% CI 43–63) patients presented erectile dysfunction according to the IIEF-15 questionnaire: 19.3% suffered from severe erectile dysfunction, 10.2% from moderate erectile dysfunction and 23.9% from mild erectile dysfunction. There was a good correlation between an affirmative answer to the direct question of whether they were impotent and erectile dysfunction defined by the IIEF-15 questionnaire (OR

Table 2. Risk factors associated with erectile dysfunction.

Factor	Erectile dysfunction ($n=47$)	No erectile dysfunction ($n=41$[‡])	OR (95% CI)	*P*
Age (years); mean ± SD	44.2 ± 8.4	39.8 ± 7.4	2.05 (1.2–3.6)[1]	0.014*
CDC stage, % (*n*)				
A	28 (59.6)	58.5 (24)	1	
B	21.3 (10)	24.4 (10)	0.85 (0.3–2.4)	0.77
C	19.1 (9)	17.1 (7)	1.1 (0.35–3.4)	0.86
Duration of HIV (years); mean ± SD	8.6 ± 5.5	7 ± 5.8	1.6 (0.8–3.5)[1]	0.2
Nadir $CD4^+$ cell count (cells/μl); median (P_{25}–P_{75})	201 (108–250)	206 (124–374)	0.99 (0.99–1.001)	0.12
Current $CD4^+$ cell count (cells/μl); median (P_{25}–P_{75})	458 (328–596)	502 (377–772)	0.99 (0.99–1.001)	0.19
Viral load, RNA/ml; median (P_{25}–P_{75})	39 (39–91)	39 (39–452)	1 (1–1)	0.29
Group, % (*n*)				
Naive	10.6 (5)	22 (9)	1	
NN	42.6 (20)	39 (16)	2.25 (0.63–8)	0.21
PI	46.8 (22)	39 (16)	2.48 (0.7–8.8)	0.16
Exposure (years); mean ± SD				
Total ART	5.8 ± 3.5	5.2 ± 3.6	1.08 (0.97–1.2)	0.17
Non-NRTI	2.8 ± 2.1	3.3 ± 2.3	1.05 (0.9–1.3)	0.58
NRTI	10.1 ± 7.4[§]	8.1 ± 7.6	1.05 (0.9–1.2)	0.47
PI	5.7 ± 3.5	2.9 ± 2.3	1.19 (1.02–1.4)	0.029*
Alcohol consumption, % (*n*)				
Yes	38.3 (18)	48.8 (20)	0.65 (0.28–1.52)	0.32
SDU	9.2 ± 8.6	8.5 ± 7.3	1.012 (0.93–1.1)	0.77
Smoker, % (*n*)				
Yes	63.8 (30)	65.9 (27)	0.79 (0.3–2)	0.64
Sedentary lifestyle, % (*n*)				
Yes	56.8 (25)	58.3 (21)	0.94 (0.38–2.3)	0.89
Beck depression, % (*n*)				
Absent	55.3 (26)	68.3 (28)		
Mild	29.8 (14)	24.4 (10)		
Moderate	6.4 (3)	7.3 (3)		
Severe	8.5 (4)	–	2.22 (0.53–9.2)[†]	0.27
AMS, % (*n*)				
Yes	70.2 (33)	56.1 (23)	1.85 (0.77–4.44)	0.17
ADAM, % (*n*)				
Yes	72.3 (34)	56.1 (23)	2.05 (0.84–4.97)	0.11
TT (ng/ml); mean ± SD	4.9 ± 1.6	5.3 ± 1.2	0.86 (0.64–1.17)	0.35
Hypogonadism, % (*n*)				
TT <3 ng/ml	6.4 (3)	–	1.93 (1.57–2.37)	0.24
BMI (kg/m^2); mean ± SD	25 ± 3.64	24.4 ± 3.2	1.06 (0.94–1.2)	0.34
WHR, mean ± SD	0.95 ± 0.08	0.94 ± 0.06	25.9 (0.05–13175)	0.3
Lipodystrophy, % (*n*)				
Yes	54.3 (25)	36.6 (15)	1.99 (0.79–5.03)	0.14
TC (mg/dl); mean ± SD	186.3 ± 41.8	190.7 ± 43.9	0.98 (0.9–1.1)[2]	0.63
LDL (mg/dl); mean ± SD	127.2 ± 38	126.3 ± 44.7	1.01 (0.9–1.1)[2]	0.91
HDL (mg/dl); mean ± SD	49.3 ± 12.7	48.8 ± 16.3	1.03 (0.8–1.4)[2]	0.85
TG (mg/dl); median (P_{25}–P_{75})	137 (90–195)	149 (106–221)	0.98 (0.9–1)[2]	0.26

Data are expressed in ng/ml × 3.467 nmol/l (TT), mg/dl × 0.0258 nmol/l (total, LDL and HDL cholesterol), and mg/dl × 0.01129 nmol/l (TG). NN, current ART with two to three NRTIs along with a non-NRTI and never received PIs; P_{25}–P_{75}, 25th–75th percentiles; PI, current ART with two to three NRTIs along with an enhanced PI. ADAM, Androgen Deficiency in Aging Men; AMS, Aging Male's Symptoms Scale; ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; CI, confidence interval; EF, erectile function; HDL, high-density lipoprotein; IIEF, International Index of Erectile Function; LDL, low-density lipoprotein; NRTI, nucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor; SDU, standard drink units per week; TC, total cholesterol; TG, triglycerides; TT, total testosterone; WHR, waist–hip ratio.

*$P < 0.05$.

[†]No mild depression vs. moderate-to-severe depression.

[§]NRTI recorded as sum of exposure; [1]per decade; [2]per 10 mg/dl.

[‡]Two patients did not correctly complete EF domain of the IIEF questionnaire.

3.9, $P < 0.01$), although 43.3% of the patients who said they were not impotent had a certain degree of erectile dysfunction. Eleven patients had used 5-phosphodiesterase inhibitors, and in nine (81%) patients, they had been effective. The mean total testosterone in patients with erectile dysfunction was 4.9 ± 1.6 ng/ml, and there were no significant differences in total testosterone concentrations between patients with different degrees of erectile dysfunction.

Factors associated with erectile dysfunction in the univariate analysis are shown in Table 2. An analysis restricted to patients in the higher quartile of time of HIV infection (12.3 years) and of exposure to non-NRTI (58 months) or to a NRTI (sum of exposure 178.2 months) did not show an increased risk of erectile dysfunction. However, in this subgroup, age more than 47 years (OR 3.96, 95% CI 1.4–11.2, $P = 0.01$) and exposure to protease inhibitor for more than 79 months (OR 9.47, 95% CI 1.2–78.4, $P = 0.037$) were associated with an increased risk of erectile dysfunction. Multivariate analysis confirmed an independent association with age (per decade; OR 2.2, 95% CI 1.04–4.5, $P = 0.04$) and exposure to protease inhibitor (per year; OR 1.6, 95% CI 1.12–2.4, $P = 0.01$) (Fig. 1). This association was not modified when duration of exposures to non-NRTI and NRTI were included in the multivariate analysis. The use and duration of exposure to different NRTIs was not associated with the presence of erectile dysfunction.

Risk factors for the five sexual dysfunction domains assessed in the IIEF-15 questionnaire are shown in Table 3. The older the patients, the lower is the score on all the domains studied. Longer exposure to protease inhibitor leads to a lower score of erectile function, orgasmic function and sexual desire, whereas lipodystrophy was associated with decreased erectile function and intercourse satisfaction. Depression was associated with a lower erectile function ($P < 0.05$) and lower scores on the other domains were evaluated, and this was almost statistically significant. No impact on sexual function was detected for longer duration of the disease, a more advanced clinical stage, lower nadir $CD4^+$ cell count, alcohol consumption, sedentary lifestyle, lower total testosterone concentration or hypogonadism. Multivariate linear regression analysis of the predictive variables for the five sexual function domains is shown in Table 4.

Discussion

Erectile dysfunction is common in HIV-infected men. The prevalence of erectile dysfunction in our study has been 53.4%, similar to that obtained in other HIV-infected cohorts [7,8,13,24]. As older age has been found to be an independent predictor of erectile dysfunction, with the improving survival of this population, the prevalence may increase in the future.

The design of our study allows to interpret the effect of drug history and to limit confounding factors. The only variable in the multivariate logistic regression analysis related to ART, which was associated with erectile dysfunction, was duration of exposure to protease inhibitor. The treatment group, total ART exposure or therapy with non-NRTI or NRTI did not influence the incidence of erectile dysfunction, even in patients with a long time on ART (>102.7 months). Despite the lack of agreement on the role of ART on erectile dysfunction, data supporting some impact of antiretroviral drugs in erectile dysfunction appear to outnumber the results suggesting the opposite [24]. Regarding specific antiretrovirals, protease inhibitors [10,11,25,26], and especially indinavir [11,25] and ritonavir [10,11], are the agents most commonly involved in sexual dysfunction.

A prospective study [7] including 300 men found no association between erectile dysfunction and therapy with

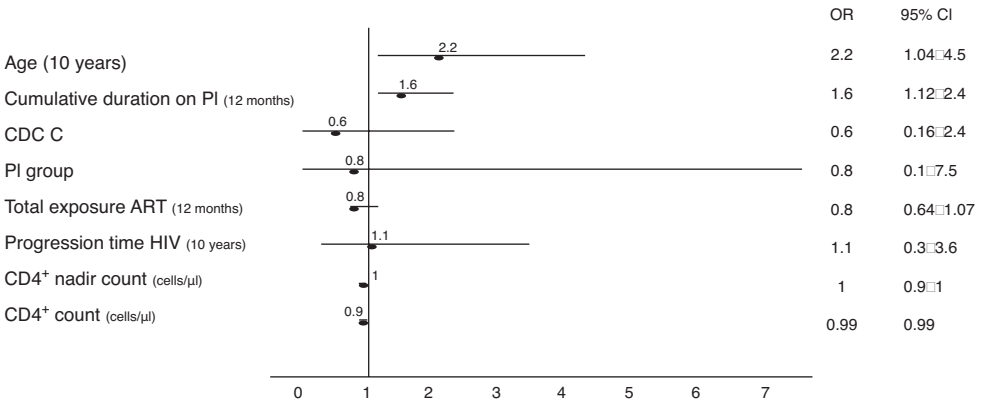

Fig. 1. Risk factors associated with erectile dysfunction in multivariate logistic regression model. Error bars are 95% CI. ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; CI, confidence interval; OR, odds ratio; PI, protease inhibitor.

Table 3. Factors related to the different sexual function domains.

	Erection		Orgasm		Intercourse satisfaction		Sexual desire		Overall satisfaction	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Age (years)	0.39	***0.000***	0.35	***0.001***	0.22	***0.04***	0.21	***0.04***	0.27	***0.04***
Duration of HIV (years)	0.16	*0.1*	0.21	*0.05*	0.12	*0.2*	0.11	*0.3*	0.07	*0.5*
Nadir $CD4^+$ cell count (cells/μl)	0.2	*0.05*	0.2	*0.07*	0.14	*0.2*	0.04	*0.7*	0.15	*0.1*
Current $CD4^+$ cell count (cells/μl)	0.2	*0.06*	0.13	*0.2*	0.15	*0.1*	0.23	***0.03***	0.06	*0.56*
Viral load (log_{10} RNA HIV)	0.12	*0.27*	0.24	***0.02***	0.07	*0.5*	0.04	*0.6*	0.13	*0.2*
Exposure (months)										
Total ART	0.18	*0.09*	0.25	***0.02***	0.11	*0.3*	0.17	*0.1*	0.14	*0.2*
Non-NRTI	0.06	*0.56*	0.12	*0.2*	0.01	*0.9*	0.16	*0.1*	0.13	*0.2*
NRTI	0.12	*0.32*	0.15	*0.2*	0.07	*0.5*	0.16	*0.1*	0.08	*0.5*
PI	0.25	***0.02***	0.25	***0.02***	0.17	*0.1*	0.23	***0.03***	0.18	*0.09*
Alcohol (SDU)	0.03	*0.8*	0.03	*0.8*	0.03	*0.8*	0.27	*0.1*	0.19	*0.2*
Smoker (packet/years)	0.27	***0.02***	0.15	*0.2*	0.17	*0.2*	0.23	*0.06*	0.23	*0.06*
TT (ng/ml)	0.09	*0.42*	0.15	*0.1*	0.17	*0.1*	0.04	*0.6*	0.01	*0.9*
BMI (kg/m^2)	0.12	*0.28*	0.04	*0.6*	0.06	*0.5*	0.28	***0.009***	0.25	***0.02***
WHR	0.24	***0.03***	0.21	*0.05*	0.2	*0.06*	0.21	*0.05*	0.23	***0.03***

	Erection		Orgasm		Intercourse satisfaction		Sexual desire		Overall satisfaction	
	Median (P_{25}–P_{75})	*P*	Median (P_{25}–P_{75})	*P*	Median (P_{25}–P_{75})	*P*	Median (P_{25}–P_{75})	*P*	Median (P_{25}–P_{75})	*P*
CDC stage		*0.6*		*0.17*		*0.3*		*0.05*		*0.39*
A	25 (14–29)		10 (8–10)		11 (8–13)		7 (6–9)		8 (7–9)	
B	25 (13–29)		10 (7–10)		10 (5–11)		6 (6–8)		8 (5–9)	
C	19 (8–27)		8 (6–10)		9 (6–12)		6 (4–7)		7 (5–8)	
Treatment group		*0.18*		***0.01***		*0.23*		*0.4*		*0.14*
Naive	27 (20–30)		10 (10–10)		12 (7–13)		7 (6–10)		8 (7–9)	
NN	24 (14–28)		9 (8–10)		10 (7–13)		7 (6–9)		8 (5–9)	
PI	19 (10–28)		9 (6–10)		10 (6–11)		7 (6–8)		7 (5–8)	
Alcohol consumption		*0.29*		*0.44*		*0.32*		*0.58*		*0.95*
No	21 (13–28)		10 (8–10)		10 (6–12)		7 (6–9)		8 (6–9)	
Yes	26 (17–29)		9 (7–10)		11 (8–13)		7 (6–9)		8 (6–8)	
Smoker		*0.96*		*0.96*		*0.6*		*0.51*		*0.24*
No	24 (14–28)		9 (8–10)		10 (7–12)		7 (6–8)		8 (7–10)	
Ex-smoker	27 (13–29)		9 (7–10)		11 (9–12)		6 (4–9)		8 (7–8)	
Yes	24 (13–29)		9 (7–10)		10 (6–13)		7 (6–9)		7 (6–8)	
Physical exercise		*0.29*		*0.41*		*0.21*		*0.25*		*0.11*
No	23 (10–28)		9 (6–10)		10 (5–12)		7 (6–8)		7 (6–8)	
Yes	24 (18–29)		9 (8–10)		11 (9–12)		7 (6–9)		8 (6–9)	
Beck depression		***0.02***		*0.28*		*0.05*		*0.06*		*0.11*
No	26 (19–29)		9 (8–10)		11 (8–13)		7 (6–9)		8 (6–9)	
Yes	17 (8–28)		9 (6–10)		10 (2–11)		5 (5–8)		7 (5–8)	
AMS		***0.03***		***0.01***		*0.05*		*0.16*		***0.02***
No	27 (19–29)		10 (8–10)		11 (8–13)		7 (6–9)		8 (7–9)	
Yes	23 (10–28)		9 (6–10)		10 (6–12)		7 (6–9)		7 (5–8)	
ADAM		***0.01***		***0.04***		***0.01***		***0.00***		***0.01***
No	28 (20–30)		10 (8–10)		12 (9–13)		8 (7–10)		8 (8–10)	
Yes	21 (10–27)		9 (7–10)		10 (5–11)		6 (6–7)		7 (6–8)	
Hypogonadism		*0.18*		*0.69*		*0.46*		*0.25*		*0.11*
No	25 (14–29)		9 (8–10)		10 (7–12)		7 (6–9)		8 (6–9)	
Yes	16 (8–ND)		9 (4–ND)		6 (0–ND)		5 (5–ND)		4 (1–ND)	
Lipodystrophy		***0.04***		*0.06*		***0.04***		*0.6*		*0.12*
No	26 (17–29)		10 (8–10)		11 (9–13)		7 (6–8)		8 (6–9)	
Yes	18 (10–27)		9 (4–10)		9 (5–11)		7 (6–9)		7 (4–8)	

Bivariate linear regression analysis (*r*, Pearson's correlation; *P*, statistical significance, in italics, $P < 0.05$ values are marked in italic-bold); ANOVA was done by Mann–Whitney *U* and Kruskal–Wallis tests. Data are expressed in ng/ml × 3.467 nmol/L (TT). NN, current ART based on two to three NRTIs along with a non-NRTI and never received treatment with PIs; P_{25}–P_{75}, 25th–75th percentiles; PI, current ART based on two to three NRTIs along with an enhanced PI. ADAM, Androgen Deficiency in Aging Men; AMS, Aging Male's Symptoms Scale; ART, antiretroviral therapy; ANOVA, analysis of variance; CDC, Centers for Disease Control and Prevention; ND, not defined; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SDU, standard drink units per week; TT, total testosterone; WHR, waist–hip ratio.

protease inhibitor or ART in the multivariate analysis, despite the highly significant association found between duration of ART and duration of use of protease inhibitor in the univariate analysis. A cross-sectional study [8] – with a low statistical power – failed to find differences in erectile dysfunction between patients treated with ART and those who were not. A cross-sectional study of 156 ambulatory HIV-infected homosexual or bisexual men suggested that actual protease inhibitor-based therapy does not seem to increase sexual dysfunction [27]. Finally, another cross-sectional study [14] of 78 homosexual men did not found differences between ART groups; however, most of the patients attributed their sexual dysfunction to ART.

With regard to studies that support the role of ART on erectile dysfunction, two retrospective studies [10,26] found an association between protease inhibitors and sexual dysfunction. The largest study [11] on this topic, with 900 patients in 10 European countries, found that the percentage of erectile dysfunction and decrease in sexual desire were greater in patients receiving protease inhibitor than in protease inhibitor-naive patients (34 vs. 12% for erectile dysfunction and 40 vs. 16% for low libido, respectively).

Three studies have used the IIEF questionnaire, as we did, to diagnose erectile dysfunction. In a cross-sectional study [8], no differences were found among the three treatment groups evaluated (with protease inhibitor 71%, without protease inhibitor 65% and no protease inhibitor in the previous 4 weeks 74%). Another large, multinational study [28] of 668 men using this questionnaire found that erectile dysfunction was associated with duration of ART, although there was no association with any specific drug. Finally, a cross-sectional study [12] of 334 men classified into three groups (ART-naive, ART with protease inhibitor and ART without protease inhibitor) found no significant association between treatment regimen and erectile dysfunction; in the multivariate analysis, treatment with indinavir was found to be an independent predictive factor of erectile dysfunction; the low prevalence of erectile dysfunction in this study, found in only 30 patients, is remarkable.

The differences found in the various studies may be explained by their different design, the population included and the tools used to evaluate erectile dysfunction. Our design allowed to eliminate past exposure to protease inhibitor as a confounding factor when determining the effect of specific antiretroviral drugs on development of erectile dysfunction, to evaluate duration of exposure to protease inhibitor and to use a validated tool (IIEF) to diagnose the main study variable. The finding of some degree of erectile dysfunction in 43.3% of the patients who answered that they were not impotent justifies the need to use validated tests in observational studies and in everyday clinical practice.

In the HIV-infected population, high sex hormone-binding globulin (SHBG) concentrations resulting in falsely increased total testosterone levels have been reported, leading to a significant underestimation of the diagnosis of hypogonadism [15,29]. So, total testosterone concentration is not useful for hypogonadism diagnosis in HIV-infected men. Nevertheless, all patients with hypogonadism in our sample presented erectile dysfunction.

There is a clear association among social (interpersonal relationships), psychological (depression, stress and anxiety) and biological factors that may interact producing a negative effect on sexual function [13,30,31]. In our population, despite the absence of differences in the prevalence of depression between those with and without erectile dysfunction (44.7 vs. 31.7%, $P = 0.2$), a moderate-to-severe depression implied a lower score on the five sexual function domains. This association with the erectile function domain was maintained in the multivariate analysis, thus demonstrating its relevance in sexual dysfunction in these patients.

The involvement of age, duration of exposure to ART, treatment group, viral load, packet/years of cigarettes, BMI, WHR, $CD4^+$ cell count and lipodystrophy as risk factors associated with a lower score on the various sexual dysfunction domains confirm the multifactor etiology of the condition.

Despite the lack of randomized clinical trials on the efficacy of phosphodiesterase type 5 inhibitors (PDE5i) in the HIV population with erectile dysfunction, PDE5 is considered to be the first choice of treatment for erectile dysfunction in HIV-infected men, provided hypogonadism has been ruled out. In our population, this therapy was not widely used, although its effectiveness was well over 80%.

This study has some limitations. The sample is limited, and there was no control group to directly compare prevalence and predictors of dysfunction; however, there is plenty of information about general population that can be used for comparisons. This was a cross-sectional study, and prospective studies may be useful to examine the incidence of erectile dysfunction and to identify temporal risk factors. Finally, evaluation of hypogonadism by means of total testosterone has multiple limitations in this population group; calculated free testosterone should be determined to adequately study gonadal function in these patients [29].
Erectile and sexual dysfunctions are very common in HIV-infected men. Age and exposure to protease inhibitor are the only predictors of erectile dysfunction in this population. The high prevalence of erectile dysfunction in initial stages of HIV infection and the absence of good clinical markers justify early routine erectile dysfunction screening in HIV-infected men. IIEF questionnaire is proposed as the first step for evaluation. Psychological welfare and depression play an important role in the development of sexual dysfunction in HIV-infected men.

Table 4. Multivariate linear regression models of predictive factors for the different sexual function domains.

	B (95% CI)	r^2	*P*
Erection (EF)		0.33	**0.004**
Age (decades)	−2.86 (−6.4 to 0.68)		0.11
PI exposure (months)	−0.65 (−1.3 to 0.05)		0.07
Smoking (packet/years)	−0.07 (−0.2 to 0.09)		0.36
WHR	11.32 (−25.3 to 47.9)		0.54
Depression	**−5.1 (−9.8 to −0.27)**		**0.039**
AMS, positive	1.5 (−4.3 to 7.29)		0.6
ADAM, positive	−4.1 (−9 to 0.9)		0.11
Lipodystrophy	−0.06 (−5.3 to 5.16)		0.98
Orgasm (OF)		0.2	**0.01**
Age (decades)	**−0.83 (−1.5 to −0.15)**		**0.02**
Viral load (log_{10} RNA)	0.21 (−0.4 to 0.85)		0.53
Exposure to ART (months)	0.09 (−0.1 to 0.29)		0.4
Exposure to PI (months)	−0.12 (−0.4 to 0.14)		0.37
Treatment group	−0.31 (−1.5 to 0.84)		0.6
AMS, positive	−0.87 (−2 to 0.29)		0.14
ADAM, positive	−0.02 (−1.1 to 1.11)		0.97
Intercourse satisfaction		0.1	**0.04**
Age (decades)	−0.82 (−2.2 to 0.52)		0.23
ADAM, positive	−1.71 (−3.9 to 0.46)		0.12
Lipodystrophy	−0.95 (−3.3 to 1.39)		0.42
Sexual desire		0.33	**0.000**
Age (decades)	−0.09 (−0.5 to 0.37)		0.68
Current CD4 cell count (100 cells/μl)	0.12 (−0.01 to 0.25)		0.08
Exposure to PI (months)	−0.06 (−0.2 to 0.06)		0.34
BMI (kg/m^2)	**−0.12 (−0.2 to −0.01)**		**0.037**
Depression	0.69 (−0.07 to 1.45)		0.08
ADAM, positive	**−1.48 (−2.3 to −0.69)**		**0.00**
Overall satisfaction		0.09	0.19
Age (decades)	−0.11 (−0.1 to 0.77)		0.8
BMI (kg/m^2)	−0.06 (−0.3 to 0.17)		0.61
WHR	−4.99 (−17.4 to 7.48)		0.43
AMS, positive	−0.55 (−1.9 to 0.85)		0.43
ADAM, positive	−0.69 (−2.1 to 0.72)		0.33

Dependent variables and statistical significance results are in bold; predictive variables are in normal type. *B*, standardized coefficient; r^2, coefficient of determination. ADAM, Androgen Deficiency in Aging Men; AMS, Aging Male's Symptoms Scale; ART, antiretroviral therapy; CI, confidence interval; EF, erectile function; OF, orgasmic function; PI, protease inhibitor; WHR, waist–hip ratio.

Further studies are necessary to evaluate the true role of hypogonadism in sexual dysfunction using calculated free testosterone concentration, as well as prospective studies to analyze the role of erectile dysfunction in HIV-infected men as an early marker of underlying macroangiopathy and endothelial dysfunction.

Acknowledgements

This study has received funding from the Spanish Foundation for Research and Prevention of AIDS (FIPSE).

O.M.-P., C.E. and C.S.-C. have carried out the study design, medical evaluation, analysis and publication of results. J.P. and A.P. did the coordination of design, recruitment of study participants, analysis and publication of results. V.B., E.M. and S.R. did the recruitment of patients. R.A. did the supervision and analytical sample collection, quality control and processing of biological samples obtained. J.S.-P. did the study design and statistical analysis supervision.

The authors have no conflict of interest.

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