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Determinants of sexual function in men living with HIV younger than 50 years old: Focus on organic, relational, and psychological issues

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Abstract

Background: Sexual dysfunctions, particularly erectile dysfunction, are common in men living with HIV, whose organic and psychological components remain to be clarified. The aim of the study is to investigate the impact of risk factors of sexual dysfunctions, including organic, relational, and psychological determinants of erectile function, in men living with HIV younger than 50 years old.

Methods: A cross-sectional, observational study was conducted in men living with HIV < 50 years. The questionnaire International Index of Erectile Function-15 was used to assess the prevalence and degree of erectile dysfunction. The structured interview of erectile dysfunction was used to explore the organic (Scale 1), relational (Scale 2), and psychological (Scale 3) components of erectile dysfunction. Total testosterone, estradiol, and dihydrotestosterone were measured by liquid chromatography-tandem-mass spectrometry; free testosterone was calculated by the Vermeulen equation.

Results: A total of 313 consecutive men living with HIV were prospectively enrolled (median age 47.0 years; median HIV-infection duration 16.2 years). 187 patients (59.7%) had erectile dysfunction, with a higher prevalence of non-heterosexual (138 out of 187, 73.8%) than heterosexual patients ($p = 0.003$). Patients with erectile dysfunction showed a worse score of structured interview of erectile dysfunction scale 3 compared to patients without erectile dysfunction ($p = 0.025$); the International Index of Erectile Function-15 was inversely related to structured interview of erectile dysfunction scale 3 ($p = 0.042$). No difference was found for sex steroids (total testosterone, estradiol, free testosterone, and dihydrotestosterone) between men living with HIV with and without erectile dysfunction. In the multivariate analysis sexual orientation, and lack of stable relationships were major determinants for erectile dysfunction.

Only 35 of 187 patients with erectile dysfunction (18.7%) reported the use of erectile dysfunction medications.

Conclusions: Within the multidimensional network of erectile dysfunction in men living with HIV, the psychological component is predominant, highlighting the contribution of peculiar factors related to HIV distress (e.g., fear of virus transmission, stigma) rather than gonadal status and other classical risk factors. In contrast to the high prevalence, only a few patients reported the use of erectile dysfunction medications suggesting a general under-management of such issues.

KEYWORDS
erectile dysfunction, HIV, libido, MSM, psychological discomfort, sexual dysfunction

1 | INTRODUCTION

Sexual dysfunction, consisting mainly of low sexual desire (SD) and erectile dysfunction (ED), is common in men living with HIV (MLWH).[1–3] Since sexual health is a primary component of well-being,[4,5] it might significantly contribute to the suboptimal quality of life.[6]

ED is a multidimensional condition defined as the inability to achieve or maintain a penile erection to be adequate enough for a satisfying sexual performance.[7,8] The prevalence of overt ED in MLWH is 13%–86%,[3] higher than the age-matched general population,[1,2,9,10] reaching up to 70% in men over 70 years old and being uncommon before 50 years old.[11,12] In addition to traditional risk factors for ED such as age, lifestyle, neurological, cardiovascular, and endocrine diseases (i.e. hypogonadism),[8,13] several HIV-related factors play a role in the pathogenesis of ED in MLWH,[2,3,14,15] including HIV per se,[9,10] duration of HIV infection and antiretroviral therapy (ART).[16–18] Additionally, earlier onset of comorbidities, premature aging, and frailty in MLWH may also be related to ED.[2,3,15–18]

In MLWH psychological domains deal with the fear of HIV transmission during sexual activity, social and cultural aspects of men who have sex with men (MSM), the stigma of the disease, and the low satisfaction of body image.[15,19–22] Nevertheless, the contribution of different risk factors to ED in MLWH and their relation with different ED components (organic, relational, psychogenic) have not been extensively investigated so far.[14,23]

From a physiological perspective, erectile function (EF), SD, and morning erections are androgen-dependent,[8,24] the latter two being strongly dependent on circulating testosterone.[24–26] Differently from HIV-uninfected men, the EF does not associate with serum testosterone in MLWH in several retrospective studies, while the association remains for SD even though weaker than expected.[27–31]

The aim of the study is to investigate the prevalence and risk factors of multiple sexual dysfunctions including organic, relational, and psychological determinants of EF, orgasmic function, SD, and morning erections in MLWH younger than 50 years old.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This was a cross-sectional observational study of prospectively collected data from May 2013 to December 2017, previously described elsewhere,[29] enrolling MLWH consecutively attending the Modena HIV Metabolic Clinic (MHMC).

Inclusion criteria were a documented HIV infection on ART treatment, age 18–50 years, and written informed consent. The choice to restrict the age range to less than 50 was made to limit all those factors involved in the pathogenesis of ED that is related to aging. Exclusion criteria were: severe liver or renal insufficiency, active malignancy, an acquired immunodeficiency syndrome (AIDS), endocrine disease (pituitary, thyroid, testicular diseases), any medication that could interfere with gonadal function as well as any previous treatment involving pituitary region (surgery, radiotherapy).

Note that, 319 MLWH were assessed for eligibility, and six were excluded from the study (one patient with severe liver insufficiency; one patient with severe chronic kidney disease; one patient with prior androgen treatment; three patients with missing questionnaires for sexual function). Finally, a total of 313 patients were enrolled.

2.2 | Sexual function assessment

Sexual function was assessed through two validated questionnaires for ED: the International Index of Erectile Function-15 (IIEF-15) and the structured interview on erectile dysfunction (SIEDY) and 2 semi-structured interviews for other sexual function domains.

IIEF-15 is the most used tool in clinical practice to investigate the presence of ED.[32] IIEF-15 is a self-reported questionnaire that investigates the five domains of male sexual function in the last month: EF, orgasmic function, SD, intercourse satisfaction, and overall satisfaction with sex life. The score is structured on a 5-point scale (from the worst

1 to the best score of 5) and a cumulative score of EF domain below or equal to 25 is used to diagnose ED.[32,33] According to the score of the EF domain, the EF was classified into the following four diagnostic categories: (i) no ED (EF score = 26–30), (ii) mild ED (EF score = 17– 25), (iii) moderate ED (EF score = 11–16), and (iv) severe ED (EF = 6–10). Sexual desire, orgasmic function, intercourse satisfaction, and overall satisfaction were defined as impaired with a score below 9 at the specific IIEF-15 domains.[32,33]

SIEDY is a structured validated interview submitted by the physician; it addressed four domains of male sexual function: i) organic ED (SIEDY scale 1), ii) relational ED (SIEDY scale 2), iii) psychogenetic ED (SIEDY scale 3), and iv) ED severity (SIEDY appendix A).[34] Scale 1 with a cut-off score > 3.0 had a sensitivity of 67.9% and a specificity of 67.6% for identifying an organic component of ED[35]; a threshold score greater or equal than 2 in Scale 2 predicts couple impairment with a sensitivity of 53%[36]; scale 3 with a threshold score greater or equal than 3 predicts psychological dimension impairment with an accuracy of 69.5%.[34]

A decreased frequency of morning erections was evaluated during the medical interview and classified as follows: an estimated reduction of the frequency of 25% was considered as 'mild', 25%–50% as "moderate", 50%–75% as "severe", and >75% as 'extremely severe'.

Finally, impairment of SD (libido) was also explored with a non-validated semi-structured medical interview.

2.3 | Covariates

2.3.1 | Demographic and anthropometric variables

Demographic (age and sex) and anthropometric (weight, height, body mass index [BMI], waist, hip, and waist/hip [W/H] ratio) variables were collected on the same day of the visit at MHMC.

2.3.2 | Hormonal parameters

After overnight fasting, an intravenous cannula was inserted into an antecubital vein at 8.00 am to collect a blood sample for serum and plasma assays. The blood samples were centrifuged, and the serum was stored at −20°C until assayed.

All biochemical and hormonal measurements have been performed as previously described.[29] In particular, sex steroids (total testosterone [TT], estradiol [E2], and dihydrotestosterone [DHT]) were assayed by validated liquid chromatography-tandem mass spectrometry (LC-MS/MS).[37–39] Of the 313 enrolled patients, 71 participants were missing E2 data. FT was calculated (cFT) by using the validated Vermeulen equation from both serum TT assessed with LC-MS/MS and serum TT assessed with confidence interval (CI).[40,41]

SHBG, serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and serum prolactin (PRL) were assessed by chemiluminescent immunoassay, as previously described.[29]

According to the current Endocrine Society guidelines, a diagnosis of biochemical hypogonadism was made when serum TT was below 320 ng/dl and/or cFT was below 64 pg/ml.[42]

2.3.3 | Biochemical measurements

The following biochemical parameters were assessed by commercially available kits: glycemia, glycated hemoglobin (HbA1c), insulin, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

2.3.4 | Sexual orientation

Sexual orientation was explored with a non-validated semi-structured medical interview and patients were grouped into heterosexual and non-heterosexual. The latter were further subdivided into four subgroups: i) MSM with a preferred active attitude (A > P); ii) MSM with a preferred passive attitude (P > A); iii) MSM with similar active or passive attitude (A = P); iv) bisexual (B).

2.3.5 | HIV parameters

HIV-related variables included HIV duration, current and nadir CD4 cell count, and HIV RNA viral load.

2.3.6 | Comorbidities

At the time of the visit, each patient was assessed for comorbidities as previously described.[29] Comorbidities were defined using the European AIDS Clinical Society guidelines.[43]

2.4 | Ethics

The study protocol was approved by the North Emilia Vast Area Ethics Committee (protocol n. 1446/15), registered in ClinicalTrials.gov (Identifier: NCT03747003), and conducted in accordance with the ethical standards of the Helsinki Declaration (1975, revised in 2013). Written informed consent has been obtained from each subject.

2.5 | Statistical analysis

According to data distribution analyzed by the Kolmogorov–Smirnov test, comparisons of continuous variables were performed using the nonparametric Mann–Whitney test and Kruskal–Wallis test followed by Dunn's multiple comparison post-hoc test. Categorical variables were compared with the Chi-square test.

Linear regression was used to examine the association between continuous variables; results were expressed through β and R^2 coefficients.

Bivariate logistic regressions were used to determine potential predictive factors for different domains of sexual function. Results were

TABLE 1 Characteristics of the entire cohort and comparison between patients with and without erectile dysfunction (ED) according to the International Index of Erectile Function (IIEF)-15 erectile function domain score. Continuous variables are reported as median (interquartile range [IQR])

		Patients with ED (IIEF-15 ≤ 25)	Patients without ED (IIEF-15 > 25)	*p*-Value
***n* 313**	**n.v.**	187 (59.7%)	126 (40.3%)	
Age (years)	–	47.4 (42.9–50)	46.7 (42.4–49.2)	0.130
Sexual orientation				
Heterosexual	–	49 (15.7%)	53 (16.9%)	**<0.0001**
MSM and bisexual	–	138 (44.1%)	73 (23.3%)	
MSM (A > P)	–	25 (8.0%)	28 (8.9%)	
MSM (A = P)	–	63 (20.1%)	40 (12.8%)	
MSM (A < P)	–	41 (13.1%)	4 (1.3%)	
Bisexual	–	9 (2.9%)	1 (0.3%)	
Anthropometric variables				
BMI (kg/m^2)	18.5–25	23.8 (22.1–25.6)	23.6 (21.8–25.5)	0.634
W/H circumference ratio	<0.95	0.95 (0.90–0.98)	0.95 (0.90–0.99)	0.858
Sexual function parameters				
Impaired SIEDY scale 1 (>3)	–	64 (34.4%)	35 (27.8%)	0.217
Impaired SIEDY scale 2 (≥2)*	–	25 (17.9%)	17 (24.8%)	0.242
Impaired SIEDY scale 3 (≥3)	–	92 (49.5%)	49 (38.9%)	0.066
Reduced sexual desire	–	155 (84.2%)	84 (68.3%)	**0.001**
Reduced morning erections	–	74 (39.6%)	30 (23.8%)	**0.004**
Hormonal measurements				
LH (mIU/ml)	1.4–8.9	4.7 (3.5–6.8)	5.0 (3.6–6.6)	0.830
FSH (mIU/ml)	1.7–6.9	5.6 (4.1–8.4)	5.6 (3.6–8.0)	0.261
PRL (ng/ml)	2.1–17.7	7.5 (5.7–10.4)	7.2 (5.2–9.3)	0.092
Serum E2 (pg/ml)	<50	24.4 (19.4–30.4)	25.6 (20.3–33.6)	0.145
Serum TT (ng/dl)	>320	632.9 (498.4–781.3)	647.6 (509.8–797.5)	0.577
E2/TT		0.036 (0.030–0.047)	0.040 (0.031–0.047)	0.144
SHBG (nmol/L)	13.5–71.4	46.6 (35.1–64.3)	49.6 (35.5–68.0)	0.734
cFT (pg/ml)	>64	104.1 (82.7–134.0)	108.0 (85.8–128.5)	0.760
DHT (pg/ml)	165–679	385.7 (279.0–535.1)	343.2 (245–520.3)	0.215
Biochemical measurements				
Fasting glucose (mg/dl)	70–100	92 (86–97.5)	93 (87–98.5)	0.460
Insulin (mIU/ml)	2–23	7.95 (5.18–12.02)	7.40 (5.00–13.40)	0.872
HOMA Index	<2.5	1.69 (1.14–2.97)	1.76 (1.17–3.02)	0.854
HbA1c (mmol/mol)	20–38	34.00 (31.15–36.71)	34.00 (31.00–36.00)	0.633
Total Cholesterol (mg/dl)	<200	186 (162–214)	190 (169–222.5)	0.269
LDL Cholesterol (mg/dl)	<100	116 (97–139.5)	124 (98–144)	0.237
HDL Cholesterol (mg/dl)	>45	46 (36–56)	46 (38–52)	0.867
Tryglicerides (mg/dl)	<180	122 (86.5–183)	134 (87.5–199.5)	0.390
Lifestyle and drug use				
Smoking	–	77 (41.4%)	46 (36.5%)	0.386
Alcohol use (moderate/intense)	–	99 (52.9%)	69 (54.8%)	0.751
Opioids use	–	39 (20.9%)	25 (19.8%)	0.827

(Continues)

TABLE 1 (Continued)

		Patients with ED (IIEF-15 ≤ 25)	Patients without ED (IIEF-15 > 25)	*p*-Value
PDE-5i use	–	35 (18.7%)	10 (7.9%)	**0.008**
Psychotropic drugs use	–	25 (13.4%)	10 (7.9%)	0.135
Comorbidities and frailty				
Diabetes	–	5 (2.7%)	2 (1.6%)	0.706
Hypertension	–	37 (19.8%)	16 (12.7%)	0.101
Cardiovascular disease	–	13 (7.0%)	6 (4.8%)	0.426
Dyslipidemia	–	93 (49.7%)	60 (48.0%)	0.764
Frailty index	<0.21	0.25 (0.20–0.33)	0.24 (0.17–0.32)	0.270
HIV parameters				
HIV duration (years)	–	16.6 (8.9–23.8)	14.1 (7.5–23.7)	0.266
ART exposure (years)	–	14.5 (7.5–19.6)	13.2 (4.8–20.1)	0.140
Nadir CD4 (cells/μL)	–	252 (82–352)	250 (220–350)	0.453
Current CD4 (cells/μL)	>400	625 (507–803)	624 (514–880)	0.898
HIV undetectability (< 40 copies/ml)	–	143 (76.5%)	103 (81.8%)	0.874

Abbreviations: A = P, MSM with similarly active and passive attitude; A > P, MSM with a preferred active attitude; ART, antiretroviral therapy; B, bisexual. BMI, body mass index; cFT, calculated free testosterone; DHT, dihydrotestosterone; E2, estradiol; ED, erectile dysfunction; EF, erectile function; Fisher's exact test was used instead of Chi-square test when the sample size was less than 5. *This analysis was restricted to only patients reporting a stable relationship (196 out of 313); FSH, follicle-stimulating hormone; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; IIEF, validated International Index of Erectile Function; IQR, interquartile range; LDL, low-density lipoprotein. Mann-Whitney test and Chi-square test were used to compare continuous and categorical variables, respectively; LH, luteinizing hormone; MSM, men who have sex with men; n.v., normal values; P > A, MSM with a preferred passive attitude; PDE-5i, phosphodiesterase 5-inhibitors; PRL, prolactin; SD, sexual desire; SHBG, sex hormone-binding globulin; SIEDY, structured interview of erectile dysfunction; TT, total testosterone; W/H, waist/hip circumference ratio.

expressed through odds ratio (OR) and 95% CI. Thereafter, multivariate regression analysis using a backward elimination method was applied to the data with $p < 0.1$ as the criterion for a variable to enter the model.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software for Windows (version 27.0; SPSS Inc, Chicago, IL). For all comparisons, $p < 0.05$ was considered statistically significant.

3 | RESULTS

A total of 313 consecutive MLWH were enrolled, with a median age of 47 years (interquartile range [IQR] 25.2–50.5) and a median duration of HIV infection of 16.2 years (IQR 1.1–35.4). The clinical characteristics of the entire cohort are summarized in Table 1.

Table S1 summarizes tools used to classify the six sexual function domains analyzed in this cohort which will be described separately. The prevalence of sexual dysfunctions according to scores of IIEF-15 specific domains and SIEDY scales were reported in Figure 1.

3.1 | Erectile function

Out of 313 MLWH, 187 (59.7%) presented ED: in detail 59 had severe ED, 35 had moderate ED, and 93 had mild ED (Figure 1, Table 1, and Table S2).

Age, BMI, and lifestyle were not associated with ED or its degree (Table 1, Table S2, and Figure 2). Age was inversely related to IIEF-15 score ($R^2 = 0.020, \beta = -0.140, p = 0.013$).

No significant difference was found for hormonal measurements (TT, cFT, E2, LH, FSH, DHT, SHBG, and PRL) between MLWH with and without ED (Table 1). However, among patients with ED, serum TT and cFT were significantly lower in patients with severe ED compared to those with mild ED (Table 2). Among MLWH with ED identified as having an organic component by SIEDY both serum TT and cFT resulted to be protective for ED (Table 2) indicating that vice versa low serum T was at higher risk for the organic component. The prevalence of ED in hypogonadal and eugonadal MLWH did not significantly differ (p = 0.172); ED was found in 24 hypogonadal patients out of 34 (70.6%) presented ED, and in 162 eugonadal patients out of 279 (58.4%). However, the IIEF-15 score of EF was significantly lower in hypogonadal patients compared to eugonadal (19.5 [IQR 5.5–27] vs. 24 [IQR 15–28], $p = 0.034$).

Comorbidities did not differ in MLWH with and without ED (Table 1).

ED was more prevalent in non-heterosexual than heterosexual MLWH ($p < 0.001$) (Table 1). In detail, 41 patients with ED out of 187 (21.9%) and only four patients without ED out of 126 (3.2%) were MSM with a more frequent passive attitude ($p < 0.0001$) (Table 1). The univariate logistic regression showed that non-heterosexual MLWH had a two-fold increased likelihood to present ED compared to heterosexual MLWH (OR = 2.045; 95% CI 1.264–3.308; $p = 0.004$). Furthermore, MSM patients with a more frequent passive than active attitude had

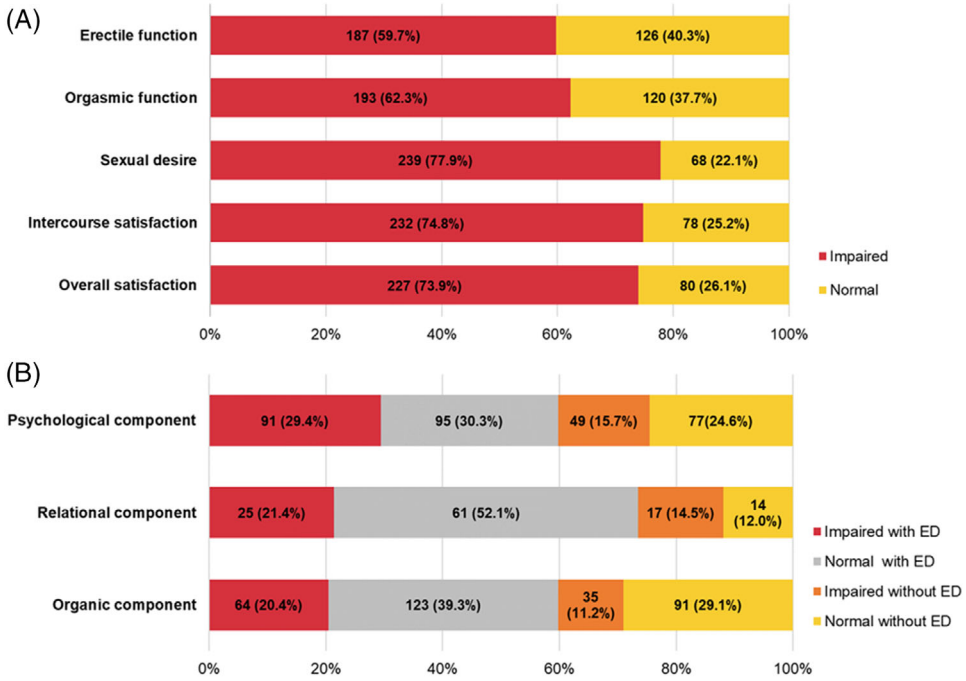

FIGURE 1 Prevalence of sexual dysfunctions according to IIEF-15 domains (A) and to SIEDY scale (B). IIEF: validated International Index of Erectile Function; ED: erectile dysfunction; SIEDY: structured interview of erectile dysfunction

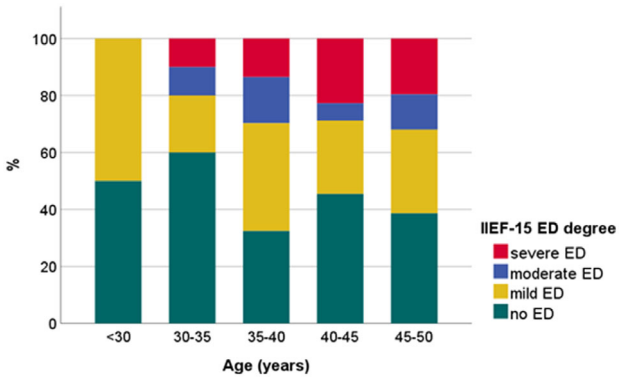

FIGURE 2 Distribution of ED severity according to patients' age range. IIEF: validated International Index of Erectile Function; ED: erectile dysfunction

an 11-fold increased likelihood to present ED compared with heterosexual men (OR = 11.087; 95% CI = 3.70–33.23; $p < 0.0001$); similarly, bisexual men had a 9-fold increased likelihood to present ED compared with heterosexual men (OR = 9.74; 95% CI = 1.12–79.67; $p < 0.0001$).

The use of phosphodiesterase 5-inhibitors (PDE-5i) was more common among MLWH with ED than MLWH without ED ($p = 0.008$). Of note, only 35 patients up to 187 with ED (18.7%) reported the use of PDE-5i. The use of PDE-5i was more common in hypogonadal (10 out of 34, 29.4%) than eugonadal MLWH (35 out of 244, 14.3%) ($p = 0.008$), whereas no difference was found in relation to the sexual orientation ($p = 0.908$).

ED was further analyzed in its 3 components according to the SIEDY scales (Table 2).

3.1.1 | Organic component of ED

According to SIEDY scale 1, 99 MLWH out of 313 (31.6%) presented an impaired organic component: of them, 64 had already developed ED, whereas 35 have not (Table 1, Figure 1). Overall, MLWH with altered organic components had an increased likelihood to present ED (OR 1.13; 95% CI: 1.01–1.27; $p = 0.028$).

Logistic analysis was performed to detect predictors of organic ED. Among demographic and anthropometric variables, age, BMI, and W/H ratio were associated with a higher risk of organic ED (Table 2). LH and FSH were positively associated with organic ED, while serum TT and cFT were inversely associated with organic ED (Table 2). As expected, insulin, HbA1c, hypertension, cardiovascular disease, and dyslipidemia were related to a greater risk of organic ED (Table 2). Among HIV variables, HIV duration only was significantly associated with organic ED (Table 2). As anticipated, the use of PDE-5i was associated with organic ED (Table 2).

3.1.2 | Relational component of ED

The presence of a stable relationship (i.e., lasting at least 2 months) was explored through item n. 5 of SIEDY. A total of 77 out of 102 heterosexual (75.5%) and 119 out of 211 non-heterosexual (56.9%) MLWH declared to be in a stable relationship, with a significant difference among the two subgroups ($p < 0.0001$). ED was more frequent among MLWH without a stable relationship (86 out of 117 patients, 73.5%) than those with a stable relationship (101 out of 196 patients, 51.5%) ($p < 0.0001$).

TABLE 2 Univariate logistic regressions with different components of erectile dysfunction (ED) (organic, relational, and psychological) as outcomes. Results are reported as odds ratio [95% confidence interval (CI)]

			ED with impaired organic component		ED with impaired relational component		ED with an impaired psychological component	
			OR [95% CI]	*p*-Value	OR [95% CI]	*p*-Value	OR [95% CI]	*p*-Value
Organic determinants	Demographic and anthropometric parameters	Age	**1.085 [1.017–1.158]**	**0.013**	**1.146 [1.014–1.297]**	**0.030**	0.981 [0.940–1.024]	0.375
		BMI	**1.154 [1.058–1.258]**	**0.001**	1.053 [0.928–1.195]	0.423	0.989 [0.919–1.065]	0.773
		W/H	**1768 [23–135,499]**	**<0.001**	67.801 [0.148–31,149]	0.178	0.431 [0.014–13.231]	0.630
	Hormonal measurements	LH	**1.056 [1.009–1.104]**	**0.018**	1.026 [0.966–1.090]	0.404	1.011 [0.969–1.054]	0.624
		FSH	**1.064 [1.022–1.108]**	**0.003**	0.991 [0.924–1.062]	0.791	1.010 [0.976–1.042]	0.562
		Prolactin	1.012 [0.975–1.049]	0.537	0.994 [0.929–1.063]	0.861	1.013 [0.981–1.047]	0.432
		SHBG	1.007 [0.997–1.017]	0.164	1.001 [0.986–1.017]	0.860	0.998 [0.990–1.007]	0.738
		Serum TT	**0.861 [0.753–0.985]**	**0.030**	1.044 [0.875–1.245]	0.632	0.923 [0.831–1.025]	0.133
		cFT	**0.890 [0.818–0.969]**	**0.007**	1.062 [0.957–1.178]	0.258	0.981 [0.921–1.044]	0.537
		Serum E2	1.021 [0.984–1.058]	0.268	0.998 [0.949–1.048]	0.923	0.979 [0.950–1.010]	0.185
		DHT	1.239 [0.291–5.281]	0.772	0.720 [0.766–7.859]	0.787	1.030 [0.323–3.282]	0.961
	Biochemical measurements	Fasting glucose	1.011 [0.998–1.025]	0.101	1.005 [0.985–1.026]	0.607	0.986 [0.967–1.005]	0.139
		Insulin	**1.041 [1.009–1.074]**	**0.011**	1.022 [0.987–1.059]	0.222	1.010 [0.983–1.037]	0.467
		HOMA Index	1.089 [0.995–1.192]	0.065	1.045 [0.959–1.139]	0.318	1.001 [0.931–1.081]	0.935
		HbA1c	**1.076 [1.024–1.132]**	**0.004**	1.038 [0.969–1.112]	0.287	0.979 [0.938–1.022]	0.341
		Total cholesterol	0.996 [0.989–1.004]	0.330	0.996 [0.986–1.006]	0.513	0.995 [0.989–1.001]	0.134
		LDL cholesterol	0.999 [0.991–1.007]	0.835	0.996 [0.984–1.008]	0.549	0.997 [0.991–1.004]	0.455
		HDL cholesterol	0.980 [0.960–1.001]	0.065	0.991 [0.959–1.025]	0.600	**0.981 [0.964–0.986]**	**0.030**
		Tryglicerides	1.000 [0.998–1.002]	0.991	1.001 [0.998–1.004]	0.515	1.001 [0.999-1.003]	0.276
	Lifestyle	Smoking	1.155 [0.661–2.019]	0.612	1.202 [0.509–2.839]	0.674	**2.000 [1.250–3.201]**	**0.004**
		Alcohol use (moderate/intense)	1.053 [0.606–1.827]	0.855	1.741 [0.713–4.250]	0.224	0.896 [0.566–1.418]	0.639
		Opioids use	1.555 [0.820–2.946]	0.176	2.186 [0.891–5.631]	0.088	0.844 [0.474–1.500]	0.563
	Comorbidities and frailty	Diabetes	3.012 [0.657–13.814]	0.156	1.740 [0.187–16.221]	0.627	0.272 [0.032–2.284]	0.230
		Hypertension	**2.975 [1.564–5.660]**	**<0.001**	**3.893 [1.574–9.630]**	**0.003**	1.346 [0.739–2.451]	0.332

(Continues)

TABLE 2 (Continued)

			ED with impaired organic component		ED with impaired relational component		ED with an impaired psychological component	
			OR [95% CI]	*p*-Value	OR [95% CI]	*p*-Value	OR [95% CI]	*p*-Value
		Cardiovascular diseases	**2.547 [1.001–6.483]**	**0.050**	2.455 [0.617–9.716]	0.202	1.228 [0.479–3.146]	0.669
		Dyslipidemia	**4.523 [2.407–8.501]**	**<0.001**	1.029 [0.442–2.397]	0.947	1.746 [0.580–1.453]	0.645
		Frailty index	**24.845 [1.513–408]**	**0.024**	17.246 [0.473–400.079]	0.076	3.819 [0.163–18.710]	0.258
	HIV parameters	HIV duration (years)	**1.051 [1.018-1.086]**	**0.003**	1.050 [0.999-1.102]	0.053	1.005 [0.979–1.032]	0.694
		ART duration (years)	**1.048 [1.010–1.086]**	**0.012**	**1.055 [1.000–1.113]**	**0.048**	0.993 [0.964–1.023]	0.641
		Nadir CD4	1.000 [0.997–1.003]	0.976	0.997 [0.993–1.002]	0.262	1.001 [0.998–1.004]	0.646
		Current CD4	0.999 [0.997–1.001]	0.410	0.998 [0.996–1.001]	0.278	1.000 [0.998–1.002]	0.685
		HIV undetectability (<40 copies)	0.343 [0.094–1.257]	0.106	0.429 [0.048–3.848]	0.449	0.275 [0.089–2.137]	0.219
Relational determinants	Sexual orientation	MSM and bisexual	1.107 [0.619–1.977]	0.732	1.505 [0.648–3.498]	0.342	**1.902 [1.137–3.181]**	**0.014**
	PDE-5i use		**2.855 [1.446–5.635]**	**0.002**	**2.778 [1.037–7.440]**	**0.042**	**2.378 [1.254–4.509]**	**0.008**
	Stable relationship		0.842 [0.480–1.476]	0.548	n.a.	n.a.	**0.383 [0.238–0.617]**	**<0.001**
Psychological determinants	Antidepressant drugs use		1.157 [0.410–3.263]	0.783	0.552 [0.069–4.440]	0.576	2.114 [0.883–5.060]	0.093
	Benzodiazepines use		0.971 [0.313–3.011]	0.959	2.037 [0.399–10.488]	0.392	0.891 [0.345–2.331]	0.811

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; cFT, calculated free testosterone; CI, confidence interval; DHT, dihydrotestosterone; E2, estradiol; ED, erectile dysfunction; FSH, follicle-stimulating hormone; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; LH, luteinizing hormone; MSM, men who have sex with men; PDE-5i, phosphodiesterase 5-inhibitors; PRL, prolactin; SHBG, sex hormone-binding globulin; TT, total testosterone; W/H, waist/hip circumference ratio.

According to SIEDY scale 2, 42 out of 196 MLWH with a stable relationship (21.4%) presented a relational impairment: of them, 25 had developed ED, whereas 17 have not (Table 1 and Figure 1). Age, hypertension, and use of PDE-5i were associated with a higher risk of relational ED in univariate analysis (Table 2).

3.1.3 | Psychological domains of ED

According to SIEDY scale 3, 141 out of 313 MLWH (45.0%) presented a psychological component for ED: of them, 92 had already ED, whereas 49 had not (Table 1, Figure 1). Patients with ED had a significantly higher score of SIEDY scale 3 compared to patients without ED ($p = 0.025$) (Table 1).

IIEF-15 score of the EF domain was inversely related to SIEDY scale 3 ($R^2 = 0.013$, $\beta = -0.115$, $p = 0.042$). Accordingly, MLWH with the compromised psychological component of erection had a nearly 1.5-fold increased likelihood to present ED (OR = 1.2, 95% CI: 1.03–1.31; $p = 0.017$).

Smoking, MSM sexual orientation, and use of PDE-5i were associated with a higher risk of psychological ED, while HDL and being in a stable relationship had a protective effect on psychological ED (Table 2).

3.1.4 | Multivariate analysis

A multivariate logistic regression analysis was performed to identify risk factors for ED and its sub-domains (data now shown for relational and psychological sub-domains not contributing to clinical interpretation). Co-variates were chosen including variables that univariate analysis displayed a p-value < 0.10. Figure 3 depicts the Forest-Plot of significant variables. The multivariate analysis showed that a reduced frequency of morning erections (OR = 2.15; 95% CI: 1.21–3.80; $p = 0.009$), MSM sexual orientation (OR = 2.42; 95% CI: 1.27–4.60; $p = 0.007$), and, marginally, use of PDE-5i (OR = 2.36; 95% CI: 1.00–5.59; p = 0.051) were risk factors for ED, whereas being in a stable relationship had a protective effect on ED (OR = 0.29; 95% CI: 0.16–0.52; $p < 0.001$) (Figure 3A). On the contrary, HIV-related variables lost statistical significance (Figure 3A). Similarly, dyslipidemia (OR = 4.36; 95% CI: 2.01–9.43; $p < 0.001$) and the use of PDE-5i (OR = 3.44; 95% CI: 1.42–8.32; $p = 0.006$) were risk factors for organic ED (Figure 3B).

3.2 | Sexual desire

Considering the IIEF-15 specific domain, 239 patients out of 313 (77.9%) presented reduced SD, while 68 patients (22.1 %) had normal desire (Figure 1). Patients with ED reported higher rates of reduced libido compared to patients without ED (Table 1).

No difference was found for hormonal parameters (TT, cFT, E2, and DHT) between patients with low libido and those not complaining of a reduction of SD. However, considering the gonadal status as a categorical variable (i.e., hypogonadism vs. eugonadism), 31 hypogonadal patients out of 34 (93.9%) reported a reduction of SD, whereas 208 eugonadal patients out of 276 (75.9%) had a reduction of SD, with a significant difference ($p = 0.018$).

The prevalence of low libido did not differ in relation to sexual orientation ($p = 0.615$). Indeed, at the logistic regression, the only parameters which reduced SD were age and smoking (Table 3).

3.3 | Morning erections

A total of 104 MLWH (33.2%) reported a reduction in morning erections. A reduction of morning erections was more frequent among patients with ED ($p = 0.004$) (Table 1).

Patients with reduced morning erections had significantly lower serum TT and cFT compared to patients not complaining of a reduction of morning erections (TT: 584 ng/dl [IQR 467–748] vs. 674 ng/dl [IQR 540–802], $p = 0.006$; cFT: 99 pg/ml [IQR 77–125] vs. 110 pg/ml [IQR 88–125], $p = 0.006$). Accordingly, the reduction of morning erection was more frequent among hypogonadal patients than eugonadal (61.8% vs. 36.9%, respectively; $p = 0.005$). At the logistic regression, increased LH, low serum TT, and low cFT were associated with a higher risk of morning erections (Table 3).

Furthermore, age, opioid use, diabetes, dyslipidemia, and HIV duration were positively associated with reduced morning erections (Table 3).

3.4 | Orgasmic function

According to IIEF-15 domain-specific for orgasmic function, 193 (61.7%) MLWH presented an orgasmic function impairment (Figure 1). None of the explored variables was found as a significant risk factor for impaired orgasmic function at the logistic regression (Table 3).

Finally, 227 MLWH (73.9%) reported an overall satisfaction impairment, according to the specific domain of IIEF-15 (Figure 1).

4 | DISCUSSION

This study provides evidence that sexual dysfunction, particularly ED, in young MLWH is a highly prevalent multidimensional disorder related to sexual orientation and psychological domains.

In our cohort, the prevalence of sexual dysfunctions was 60% for ED and up to 78% for reduced SD, in line with previous studies on ED[9,10,15,16,44–48] and reduced SD.[49] ED prevalence is 3-time higher than the age-matched (30–50 years) Italian general population (22.4%).[50]

Our study is the first to investigate the psychological domain in MLWH using the SIEDY scale 3, which is the only tool that specifically explores the presence of psychological impairment (not specific for a psychological disorder) leading to ED.[34,35] This study adds information also on the relational component of ED which is often neglected[23,54]

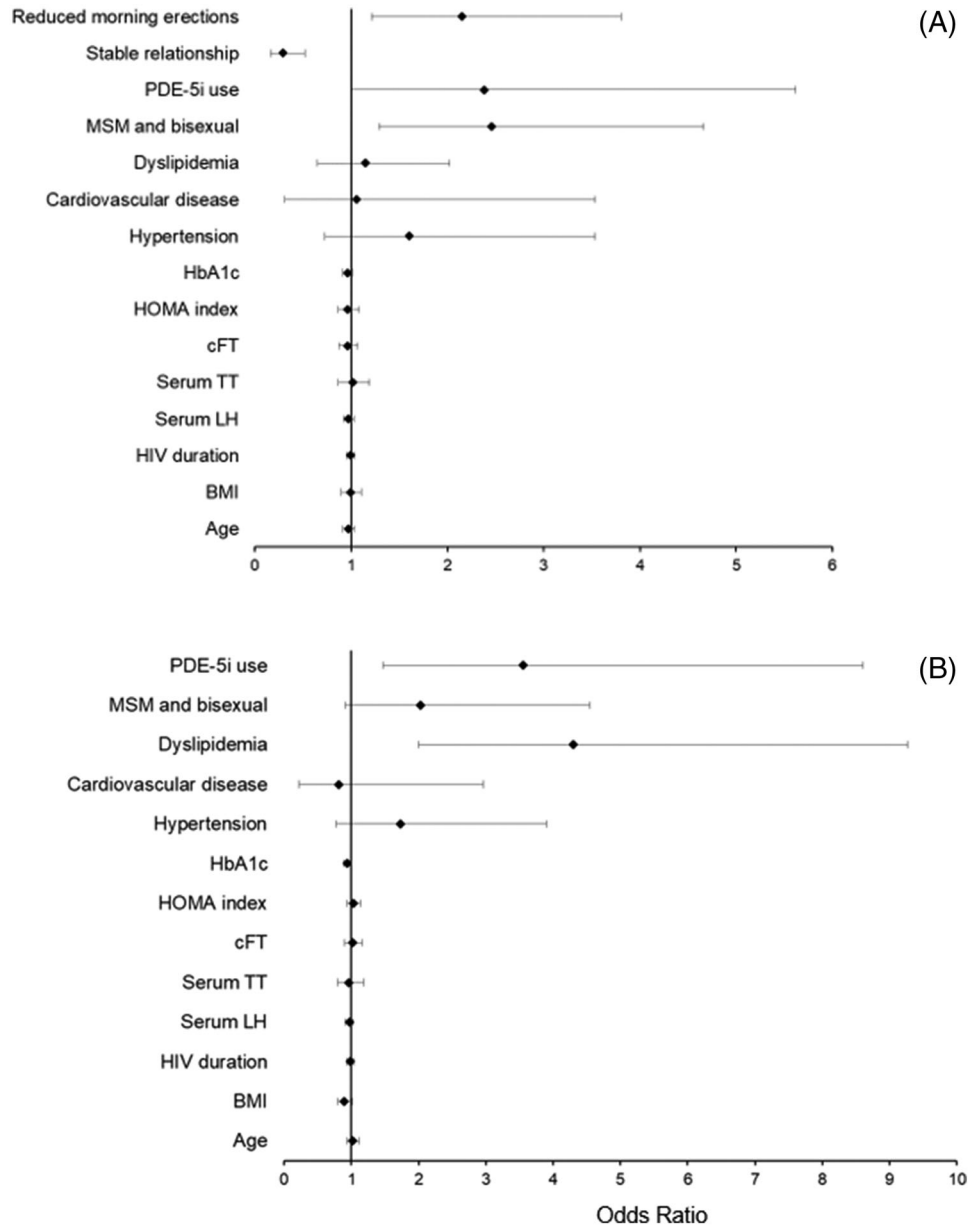

FIGURE 3 Forest-Plot for the multivariate analysis performed to identify significant determinants of ED (A) and organic ED (B). ED: erectile dysfunction; MSM: men who have sex with men; BMI: body mass index; LH: luteinizing hormone; TT: total testosterone; cFT: calculated free testosterone; HOMA: homeostasis model assessment; HbA1c: glycated hemoglobin; PDE-5i: phosphodiesterase 5-inhibitors

and suggests that the lack of a stable relationship is associated with ED in MLWH.

Another major determinant of ED is sexual orientation since MSM and bisexual MLWH have an eleven-fold and nine-fold, respectively, increased likelihood to present ED compared to heterosexual men, in line with most previous studies.[9,23,55–57] The fact that ED was associated with passive sexual attitude in MLWH confirms previous data and raises concerns about causality since it is difficult to establish if the choice of a passive sexual attitude prompts ED or vice versa.[23]

Previous studies have explored the relationship between depression and/or anxiety and ED in MLWH[10,18,45,46,48,51–53] focusing on the mere association between each of these diseases or the use of anxiolytic/antidepressants and ED. The results are, however, conflicting and no study has evaluated the psychological component intrinsic to ED in MLWH. Indeed, psychological domains in MLWH go beyond the diagnosis of anxiety/depression. Several emotional status and psychological issues are peculiar to MLWH and/or MSM and may strongly impact sexual behavior. Among them: i) the stigma and ii) changes in body image may be related to self-feeling of being less desirable and to fear to be rejected by the partner (when disclosing HIV status or when the latter is incidentally discovered); iii) the fear of HIV transmission has a possible direct impact on all components of sexual behavior; iv)

TABLE 3 Univariate logistic regressions with reduced sexual desire, impaired orgasmic function, and reduced morning erections as outcomes. Results are reported as odds ratio [95% confidence interval (CI)]

			Reduced sexual desire		Impaired orgasmic function		Reduced frequency of morning erections	
			OR [95% CI]	*p*-Value	OR [95% CI]	*p*-Value	OR [95% CI]	*p*-Value
Organic determinants	Demographic and anthropometric parameters	Age	**1.060 [1.010–1.111]**	**0.018**	0.971 [0.928–1.016]	0.199	**1.084 [1.032–1.139]**	**0.001**
		BMI	0.965 [0.887–1.050]	0.412	0.963 [0.895–1.036]	0.314	1.068 [0.992–1.149]	0.079
		W/H	0.338 [1.006–19.500]	0.600	0.037 [0.001–1.177]	0.062	27.408 [0.883–850.972]	0.059
	Hormonal measurements	LH	1.037 [0.971–1.107]	0.282	0.995 [0.954–1.039]	0.824	**1.065 [1.013–1.120]**	**0.013**
		FSH	1.046 [0.986–1.111]	0.137	0.989 [0.955–1.024]	0.524	1.021 [0.986–1.057]	0.247
		Prolactin	0.977 [0.944–1.011]	0.184	0.978 [0.946–1.012]	0.204	0.997 [0.964–1.031]	0.850
		SHBG	1.006 [0.995–1.017]	0.319	0.998 [0.989–1.007]	0.626	1.004 [0.995–1.013]	0.395
		Serum TT	0.987 [0.877–1.112]	0.832	0.939 [0.848–1.039]	0.222	**0.863 [0.774–0.962]**	**0.008**
		cFT	0.969 [0.903–1.040]	0.389	0.990 [0.931–1.053]	0.752	**0.887 [0.828–0.951]**	**<0.001**
		Serum E2	1.007 [0.973–1.042]	0.706	0.995 [0.966–1.025]	0.742	1.010 [0.981–1.040]	0.499
		DHT	1.308 [1.323–5.925]	0.707	0.767 [0.237–2.488]	0.659	1.195 [0.376–3.776]	0.762
	Biochemical measurements	Fasting glucose	1.002 [0.986–1.018]	0.829	0.995 [0.983–1.008]	0.468	1.005 [0.993–1.018]	0.416
		Insulin	0.991 [0.961–1.023]	0.590	0.999 [0.972–1.027]	0.955	1.022 [0.994–1.051]	0.127
		HOMA Index	1.000 [0.914–1.093]	0.993	1.006 [0.932–1.087]	0.874	1.040 [0.962–1.125]	0.320
		HbA1c	1.004 [0.956–1.054]	0.869	0.992 [0.952–1.033]	0.696	1.034 [0.992–1.778]	0.113
		Total cholesterol	1.002 [0.995–1.009]	0.567	0.999 [0.993–1.005]	0.789	1.000 [0.994–1.006]	0.908
		LDL cholesterol	1.007 [0.998–1.015]	0.126	1.001 [0.994–1.008]	0.708	1.004 [0.997–1.010]	0.314
		HDL cholesterol	1.007 [0.987–1.027]	0.512	1.014 [0.997–1.031]	0.110	0.988 [0.972–1.004]	0.141
		Tryglicerides	0.999 [0.997-1.001]	0.399	1.000 [0.998–1.002]	0.886	1.000 [0.999–1.002]	0.726
	Lifestyle	Smoking	**1.869 [1.037–3.368]**	**0.037**	1.682 [1.038–2.725]	0.035	1.439 [0.906–2.287]	0.123
		Alcohol use (moderate/intense)	1.388 [0.809–2.382]	0.234	1.073 [0.677–1.699]	0.765	1.309 [0.829–2.068]	0.248
		Opioids use	1.613 [0.771–3.374]	0.204	0.902 [0.512–1.590]	0.722	**1.881 [1.080–3.273]**	**0.026**

(Continues)

TABLE 3 (Continued)

			Reduced sexual desire		Impaired orgasmic function		Reduced frequency of morning erections	
			OR [95% CI]	*p*-Value	OR [95% CI]	*p*-Value	OR [95% CI]	*p*-Value
	Comorbidities and frailty	Diabetes	–	0.999	1.529 [0.292–8.012]	0.615	**9.692 [1.152–81.520]**	**0.037**
		Hypertension	0.825 [0.412–1.653]	0.587	1.349 [0.719–2.530]	0.351	1.476 [0.814–2.675]	0.200
		Cardiovascular diseases	1.451 [0.407–5.166]	0.566	0.823 [0.321–2.111]	0.686	1.780 [0.702–4.514]	0.225
		Dyslipidemia	1.624 [0.939-2.810]	0.083	1.565 [0.983-2.490]	0.059	**1.989 [1.254-3.155]**	**0.003**
		Frailty index	9.728 [0.558–169.507]	0.119	1.512 [0.140–16.316]	0.733	**31.976[2.900–352.558]**	**0.005**
	HIV parameters	HIV duration (years)	1.009 [0.978–1.041]	0.586	0.990 [0.946–1.016]	0.435	**1.051 [1.023–1.080]**	**<0.001**
		ART duration (years)	0.995 [0.962–1.030]	0.794	0.984 [0.956–1.013]	0.285	**1.042 [1.012–1.074]**	**0.006**
		Nadir CD4	0.999 [0.996–1.001]	0.308	1.009 [0.990–1.030]	0.347	0.997 [0.994–1.000]	0.060
		Current CD4	1.000 [0.998–1.002]	0.765	1.011 [0.995–1.027]	0.189	0.999 [0.997–1.001]	0.503
		HIV undetectability (<40 copies)	0.502 [0.105–2.388]	0.386	–	0.998	0.199 [0.039–1.005]	0.051
Relational determinants	Sexual orientation	MSM and bisexual	1.163 [0.646–2.092]	0.615	0.739 [0.455–1.202]	0.223	0.995 [0.613–1.614]	0.984
	PDE-5i use		0.897 [0.416–1.932]	0.780	0.856 [0.447–1.641]	0.640	3.355 [1.734–6.491]	<0.001
	Stable relationship		1.043 [0.599–1.817]	0.881	0.800 [0.495–1.291]	0.360	0.999 [0.625–1.596]	0.996
Psychological determinants	Antidepressant drugs use		3.014 [0.686–13.231]	0.144	0.867 [0.358–2.095]	0.751	1.313 [0.549–3.139]	0.541
	Benzodiazepines use		1.659 [0.472–5.838]	0.430	1.135 [0.439–2.932]	0.794	1.032 [0.409–2.602]	0.947

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; cFT, calculated free testosterone; CI, confidence interval; DHT, dihydrotestosterone; E2, estradiol; ED, erectile dysfunction; FSH, follicle-stimulating hormone; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; LH, luteinizing hormone; MSM, men who have sex with men; PDE-5i, phosphodiesterase 5-inhibitors; PRL, prolactin; SHBG, sex hormone-binding globulin; TT, total testosterone; W/H, waist/hip circumference ratio.

the obligatory use of a condom may impact on quality of erection; v) peculiar sexual behavior in MSM (e.g., casual sex group, anal penetration requiring a better erection in terms of both duration and rigidity). All these psychological aspects are well recognized in MLWH and MSM literature[2,3,22,23,57] and need to be considered by both the specialist in infectious disease and the andrologist/expert in sexual medicine. Furthermore, increasing personal and social awareness of HIV could help the implementation of proper harm reduction strategies that are recognized as important measures to improve sexual health in at-risk populations.[58]

Other HIV-related factors such as duration of infection and ART exposure contribute to increased risk of ED in these patients, but their impact is lost in the multivariate analysis.[15,23,51]

In our study classical risk factors of ED, especially cardiometabolic parameters resulted associated with organic ED and reduced morning erections, but their role was less evident in the multivariate analysis for ED where non-organic components prevailed. Differently from HIV-uninfected patients for whom classical risk factors are almost constantly associated with ED,[8,11–13,59] the strength of this association is weaker or absent in MLWH.[15,16,18,46] This means that MLWH patients affected by ED/reduced morning erections presented more vulnerability and health deficits in terms of the sum of classical risk factors,[10,60] but each of them has a minor role when taken alone in comparison to other non-quantifiable factors that are mainly related to ED in MLWH.[29] This is also the case for hypogonadism which is highly prevalent in MLWH.[27,28,30,31,61,42,62] Anyhow, when deepening the association between sex steroids and ED, both serum TT and cFT did not differ between MLWH with and without ED and they did not correlate with all IIEF-15 EF scores, except for patients identified as having an organic component of ED at SIEDY. Besides, ED prevalence did not change between eugonadal and hypogonadal MLWH. This confirms that gonadal status has a less determinant impact on ED, the latter being mainly related to androgen-independent aspects in MLWH. This is in line with previous studies obtained by us[15,27] and by other research groups.[18,51] Differently from HIV-uninfected patients where serum testosterone is almost constantly related to EF,[25,26] the lack of interrelationship between ED and androgen status seems to be a peculiar hallmark of ED in MLWH, notwithstanding the increased prevalence of hypogonadism in these patients.[27–31,61] Sexual desire, a well-known androgen-dependent issue was not associated with both serum TT and cFT in this study, thus reinforcing the role of the psychological component in MLWH since SD is also strongly dependent on the psychological status.[8] Morning erections were the only parameters that resulted to be related to TT and cFT in MLWH, confirming their strong testosterone dependency and total independency from psychological issues.[24] From a clinical standpoint, morning erections should be considered a useful surrogate of the organic (hormonal and cardiovascular) component that could be easily explored during the medical evaluation of sexual health.

The high prevalence of sexual dysfunctions in our cohort clashes with the low reported use of PDE5-i (14.4%). Although this data was obtained from a direct investigator's question to patients leading to a possible underestimation of the real use of PDE5-i, this is unlikely to be explained only by a methodological bias and suggests that ED is an undertreated and undermanaged condition in MLWH. Accordingly, this issue results be overlooked in sexual medicine research and in the clinic both in MSM[57] (who represent 67% of patients in our MLWH cohort) and MLWH in general.[2,22,23,29]

This study has strengths and limitations. The principal strength is that is the first study to explore sexual dysfunction in MLWH using different validated questionnaires (IIEF-15, SIEDY) to study both prevalence and components. Another strength is represented by the measurement of sex steroids with the gold standard LC-MS/MS. A possible limitation is the use of the IIEF questionnaire that was constructed and validated in heterosexual men. We did not use the modified IIEF for MSM[63] since only the English version is available and MLWH were enrolled regardless of their sexual preference, as in other previous studies.[16,45] Furthermore a researcher was available during questionnaire filling in case of doubts. For all these reasons, the authors do not believe that the use of IIEF-15 may have increased significantly the risk of bias. The cross-sectional study design study that does not allow for defining the cause-effect relationship. Neither the organic nor psychological components of ED were evaluated with specific tools, such as penile Doppler ultrasonography and validated psychometric instruments. However, the SIEDY questionnaire was ad hoc validated for the evaluation of each component of ED allowing us to infer the origin of ED and it could be considered a reliable first-line surrogate of other more specific investigations. The lack of a control group is another limit concerning the increased rate of prevalence of sexual dysfunction in MLWH compared to the age-matched HIV-uninfected population, but our data confirm a well-established issue.

In conclusion, our findings point out that HIV-related factors, particularly the psychological component, are predominant in the onset of ED in MLWH. A tailored clinical approach focusing on the multidimensional domains of sexual dysfunction may improve sexual health in MLWH.

AUTHOR CONTRIBUTIONS

All authors participated in the writing, editing, creation, and approval of this paper. Sara De Vincentis collected and analyzed data, provided data interpretation, and wrote the manuscript. Maria Chiara Decaroli, Jovana Milic, Flaminia Fanelli, Giulia Tartaro, Chiara Diazzi, Marco Mezzullo, Maria Cristina De Santis, Laura Roli, Tommaso Trenti, and Daniele Santi collected the data and assisted in writing. Uberto Pagotto and Giovanni Guaraldi provided data interpretation and assisted in writing. Vincenzo Rochira conceived the study, analyzed the data, provided data interpretation, and wrote the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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