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The Cumulative Effects of Medication Use, Drug Use, and Smoking on Erectile Dysfunction Among Men Who Have Sex With Men

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Abstract

Introduction—Erectile dysfunction (ED) is highly prevalent among Human Immunodeficiency Virus-seropositive (HIV+) men who have sex with men (MSM). There is a need for additional research to determine the correlates of HIV+ and HIV-seronegative (HIV−) MSM, especially regarding non-antiretroviral medication use.

Aims—This study examined the prevalence of ED and the socio-demographic, medical conditions, medication use, and substance use correlates of ED among HIV+ and HIV− MSM.

Methods—A modified version of the International Index of Erectile Function (IIEF) for MSM was self-administered by participants enrolled in the Multicenter AIDS Cohort Study (MACS), an ongoing prospective study of the natural and treated histories of HIV infection among MSM in the United States. The study sample included 1,340 participants, including 612 HIV+ and 728 HIV− men. Poisson regression with robust error variance was used to estimate prevalence ratios of ED in multivariable models in combined (HIV+/-) and separate analyses.

Main outcome measure—ED was determined by the summed scores of a modified version of the IIEF validated among MSM.

Results—Twenty-one percent of HIV+ MSM and 16% of HIV− MSM reported ED. Being >55 years of age, Black race, cumulative pack-years of smoking, cumulative antihypertensive use, and cumulative antidepressant use had significant positive associations with the prevalence of ED in the total sample. Among HIV+ men, duration of antihypertensive use and antidepressant use were

significantly associated with increasing prevalence of ED. Among HIV– men, being >55 years of age, Black race, and cigarette smoking duration were associated with increased prevalence of ED.

Conclusion—Predictors of ED may differ by HIV status.. Although smoking cessation and effective medication management may be important as possible treatment strategies for ED among all MSM, there may be a burden on sexual functioning produced by non-HIV medications for HIV + men.

INTRODUCTION

Thirty-three to 74% of HIV+ MSM have reported ED[1–3], versus a prevalence ranging from 0–18% in general population samples [4, 5]. Age may be an important predictor of ED, with an annual incidence rate in the general population of 12.4 cases per 1000 person-years for men 40–49 versus 46.4 cases per 1000 person-years for men 60–69 years old [6]. However, age is inconsistently associated with ED among HIV+ MSM [1–3]. Risk for ED also increases among men with specific health problems such as diabetes, heart disease, hypertension and depression [1,4,6]. Research is inconsistent on whether there are racial differences in ED prevalence [2, 5].

HIV-related medical conditions may also predict ED among HIV+ men. Low CD4 cell counts have been associated with ED [2]. Presence of opportunistic infections does not appear to differentiate men with and without ED [3]. Duration of antiretroviral therapy is inconsistently associated with ED [1,2]. Among HIV+ men, ED is inconsistently associated with current HIV medications [7], with some studies suggesting a relationship of protease inhibitors and ED [8, 9], but recent data from 4064 men in the Swiss Cohort Study suggesting no such relationship [10]. The relationship between presence of protease inhibitors and ED may be more complex than assessing Highly Active Antiretroviral Therapy (HAART) dichotomously, which may be too crude to reflect its true effects on ED given the differential effects of specific regimens, the prevalence of side effects and the importance of adherence on HAART efficacy and side effects. Thus, the degree of adherence to the medications may be a more revealing measure of their influence on ED in men [11].

Patients presenting with ED, especially HIV+ patients, frequently have comorbid medical conditions that have been associated with ED, such as hypertension and depression [1,2,12]. ED has been associated with multiple classes of medications such as antihypertensives and antidepressants, including among HIV+ patients [13–15]. Elevated body mass index, or BMI, may also increase ED prevalence [16].

Regarding substance use, smoking is associated with ED in the general population [4,5] and among HIV+ patients [2]. Among illicit substances, stimulant use may be associated with ED due to its deleterious effects on erection achievement and maintenance [17]. Similar to non-HIV medications, there may be a cumulative effect of smoking and use of other stimulants on ED among MSM. These variables have added significance among HIV+ MSM due to higher prevalence of depression, smoking, and stimulant drug use among HIV+ MSM than HIV– MSM populations [18–20].

Aims

The aims of the present study were to examine the prevalence of ED and the demographic, medication use, and substance use correlates of ED among HIV+ and HIV– MSM. It was hypothesized that cumulative adherence to HAART would be positively associated with ED, and that ED would be more prevalent because of cumulative years of use of non-HIV

medications (i.e., antihypertensives, antidepressants), and substance use (i.e., smoking and stimulant use).

METHODS

Study Design and Administration

Participants were enrolled in the Multicenter AIDS Cohort Study (MACS), an ongoing prospective study of the natural and treated histories of HIV infection among homosexual and bisexual men in the United States. A total of 6,972 men was recruited (4954 in 1984–1985, 668 in 1987–1991, and 1350 in 2001–2003) at four centers: Baltimore/Washington DC, Chicago, Los Angeles, and Pittsburgh. The study design has been described previously [21]. Only methods relevant to the present study are presented. MACS study protocols were approved by the institutional review boards of each of the participating centers, their community partners, and community advisory boards. Informed consent was obtained from all participants.

MACS participants return every 6 months for detailed interviews, physical examinations, and collection of blood for laboratory testing and storage in a central repository. The interview includes questions about medical conditions, medical treatments, sexual behavior, illegal drug use (including methamphetamine, marijuana, alkyl nitrites, cocaine and crack), and cigarette and alcohol consumption since the previous visit. MACS questionnaires are available at <http://www.statepi.jhsph.edu/macsfirms.html>.

Enzyme-linked immunosorbent assay with confirmatory Western blot tests were performed on all participants initially and at every semiannual visit thereafter for initially HIV-seronegative participants. T-lymphocyte subset levels were quantified by each MACS center using standardized flow cytometry [22, 23]. Self-reported use of antiretroviral medications at each visit was summarized to define to what extent participants were adherent to HAART, defined according to the DHHS/Kaiser Panel guidelines [24].

A prospective cohort design was used to examine associations between demographic variables, BMI, cigarette smoking, and use of stimulants, antihypertensives, and antidepressants with reported ED. For HIV-seropositive men, HAART use and CD4+ cell count were also included in separate models. Because ED data were collected at only visits 46 and 47 (Oct. 1, 2006 through Mar. 31, 2007), we used data at the first visit of 46 and 47 with ED data available (analysis visit) for analysis. That is, for each participant, only ED prevalence at the analysis visit and predictors of ED prevalence at the analysis visit was used in this study.

The study sample included 1,340 male participants who reported having at least one male anal intercourse sex partner since last visit, including 728 HIV-seronegative and 612 HIV-seropositive men. Also, this analysis was restricted to only White non-Hispanic, Black non-Hispanic, and Hispanic race due to a small number of participants who reported other race (n=23).

Main Outcome Measure

ED was determined by the summed scores of a modified version of 6-item Erectile Functioning scale of the International Index of Erectile Function for gay and bisexual men [25]. Men who were not sexually active received a score of 0 on 5 of the 6 questions, resulting in a range of Erectile Functioning scores from 1–30. This measure was made available to the MACS investigators by the instrument's creators before it was published. In this scale, higher scores characterize better erectile functioning during sex.

Presence of ED was defined as a score of 17 or below for participant scores on the modified scale. This score was chosen because 17.2 is 1 SD above the mean for ED samples and >1 SD below the mean of erectile functioning for normal controls.

Independent Variables

Demographic and behavior variables were included in the multivariable models to adjust for possible confounding factors. Age at the analysis visit was calculated using self-reported date of birth and was treated as a categorical covariate (<40 years (reference group), 40–44, 45–49, 50–54, ≥55 years). Race was self-reported at enrollment and categorized as White non-Hispanic (reference group), Black non-Hispanic, and Hispanic. Similar to pack years for smoking, current exposure to a medication or substance was calculated at each visit and cumulated (summed) over visits. Cumulative variables were assessed longitudinally from baseline (enrollment) to the analysis visit. Cumulative stimulant drug use was calculated for each visit as average number of reported days used per month for a period of 12 months for methamphetamine and any cocaine or crack. This involved using a measure of quantity or frequency in a given time interval depending on the wording of the particular question (the multiplier), during a given period, typically the approximately six months between visits, normalized to a yearly basis. For example, if an individual used daily during the last six months, then his current, yearly average use (for that visit) was calculated as 30.5 days per month $\times$ 0.5 years. For the drug use questions, the multipliers were daily use: multiplier=30.5 (times per month); weekly use: multiplier = 4.36; monthly use: multiplier=1; less often: multiplier=0.33. We then computed cumulative self-reported drug use by summing all yearly averages, which proceeded longitudinally from baseline (enrollment) to the analysis visit. Cigarette consumption was summarized as cumulative pack years based on the number of cigarettes smoked per day (packs/day per year). For example, if an individual smoked ≥ 1 but <2 packs per day in the last six months, then his current smoking pack years exposure was calculated as 1.5 (the average of 1 and 2) packs $\times$ 0.5 years = 0.75 pack years (pack days for one year). Similarly, additional primary exposure variables were defined as cumulative years of exposure, including cumulative antihypertensive use and antidepressant use.

Cumulative HAART adherence years was weighted by the reported adherence rate (weights were 1, 0.975, 0.85, and 0.375 for adherence 100%, 95–99%, 75–94%, and <75%, respectively). CD4+ T-cell count was used to indicate HIV disease progression among HIV + participants, and was categorized into >500, 201–500, and ≤ 200 cells/ μ l.

Data Analysis

Prevalence was calculated as the percentage of ED at the analysis visit. Poisson regression with robust error variance [26] was used to estimate prevalence ratios of ED in both univariate and multivariable models. Separate analyses were conducted for HIV+ and HIV– men, as well as the combined group using the SAS 9.2 GENMOD procedure (SAS Institute, Cary, North Carolina, USA). The covariates in the multivariable model for HIV– and the combined group included age, race, cumulative stimulant use, cumulative cigarette smoking, cumulative antihypertensive use, and cumulative antidepressant use. In addition to these factors, the multivariable model for HIV+ also included cumulative HAART adherence years and CD4+ cell count. To compare the prevalence rates for HIV+ with HIV–, an additional model was performed combining both groups. This model included the covariates for the HIV– model. Given the possible association of BMI with ED, BMI was entered as a covariate in all analyses.

RESULTS

Demographic data for HIV+ and HIV- men are provided in Table 1. The prevalence of ED was higher among HIV+ men (21%) than HIV- men (16%). The HIV- men were older (median age was 52 years) than the HIV+ men (median age was 48 years). The HIV- group had a greater proportion of white men (78%) than the HIV+ group (58%). HIV+ men had a median of 6 cumulative years of adherence (IQR, 3 to 9) to HAART. Forty-two percent of HIV+ men had CD4+ cell counts below 500 cells/ μ l.

In the multivariable models using the total sample, older age, Black race, cumulative cigarette smoking in pack-years, cumulative years of antihypertensive use, and cumulative years of antidepressant use were positively associated with ED prevalence (see Table 2). For example, in the multivariable model, being 55+ years of age was independently associated with a 60% higher prevalence of ED, Black race a 48% higher prevalence, cumulative cigarette smoking in pack-years a 7% higher prevalence, 10 cumulative years of antihypertensive use a 93% higher prevalence, and 10 cumulative years of antidepressant use a 59% higher prevalence of ED. In the multivariable model with the HIV+ sample, only cumulative years of antihypertensive use and cumulative years of antidepressant use were positively associated with ED, with a 136% and 88% increase in ED per 10 years of use, respectively. CD4+ cell count <200 cells/ μ l and cumulative cigarette smoking in pack-years were no longer associated with ED. (see Table 2). In the multivariable model with the HIV- sample, only older age (age 55+ versus age $\leq$ 40; 112% increase), Black race (88% increase), and cumulative years of cigarette smoking in pack-years (9% increase) were positively associated with ED prevalence.

We also examined the interactions between age and HIV status and between race and HIV status with ED. The interactions were not statistically significant and in both cases did not alter the pattern of findings for the main effects in the model.

DISCUSSION

We demonstrated an 18% prevalence of ED among MSM participating in the MACS, similar to a US population-based estimate of 18.4% using data from the 2001–2002 National Health and Nutrition Examination Survey (NHANES) [4]. However, the prevalence of ED was higher among the HIV+ men compared to the HIV- men in our sample, similar to other research [27]. As well, the correlates of ED differed by HIV status. For HIV+ men, only cumulative years of antihypertensive and antidepressant medication use were associated with ED prevalence among HIV+ men, whereas among HIV- men, older age, Black race, and cumulative pack-years of smoking were associated with ED prevalence. HIV medications were not associated with ED in the multivariable models.

Findings are similar to other studies with primarily non-MSM samples. ED prevalence and severity have been shown to be greater with higher versus lower dosages of antidepressants [28], and higher among hypertensive patients who were treated with antihypertensive medications than among hypertensive patients who were untreated [4]. Types of medication administered may make a difference in effective treatment for HIV+ patients with ED, because among a general sample of patients receiving antidepressant monotherapy, the odds of having ED were 4 to 6 times greater with selective serotonin reuptake inhibitors (SSRIs) or Venlafaxine XR than with bupropion [28]. For HIV- men, cumulative years of antihypertensive and antidepressant use were not significantly associated with ED prevalence, but cumulative pack-years of smoking were positively associated with ED prevalence. It is possible that for HIV+ men, age itself is less important than cardiovascular ageing associated with HIV such as atherosclerosis [29], and the added medication burden

experienced by HIV+ patients who must take antidepressants and antihypertensives in addition to HAART, may all lead to increased risks for ED.

Importantly for HIV+ men, our findings demonstrated the importance of examining factors beyond HIV medications and related conditions, such as the cumulative effects of multiple non-HIV medication use among HIV+ men. Antihypertensive and antidepressant medications are commonly prescribed to HIV+ men [30–31], and both were associated significantly with a 50% increased prevalence of ED per 10 cumulative years of use.

Given that antidepressant and antihypertensive use among HIV+ men increases the likelihood of ED, medications should be selected considering potential sexual side effects [32]. ED medication treatments are considered generally safe for cardiovascular disease patients, provided that risks are properly evaluated [33]. Adjunctive non-medication based treatments should be considered, including scientifically-based behavioral interventions to increase healthy behaviors such as exercise [34], the reduction of sodium-intake and other correlates of hypertension [35], and psychotherapies for depression such as cognitive-behavioral therapy [36].

Limitations

Although the MACS is a longitudinal study, the administration of the modified IIEF questionnaire to the 2 consecutive semiannual study visits limited us to a cross-sectional study design. Therefore we were unable to measure the incidence of ED using robust repeated measures. In addition, ED and some of the co-factors were measured by self-report, not by biological markers. More objective assessments (e.g., penile plethysmography) would have increased the validity of the definition of ED. Men taking antidepressants or antihypertensives are likely to be experiencing mental health or hypertensive conditions, respectively. Therefore, the underlying condition might be the reason for their ED, rather than the medications [37]. Future studies should attempt to rectify these limitations and retest associations with ED in other male populations.

CONCLUSION

Predictors of ED may differ by HIV status. Although smoking cessation and effective medication management may be important as possible treatment strategies for ED among all MSM, there may be a burden on sexual functioning produced by non-HIV medications for HIV+ men.

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Table 1

Characteristics of the study population

	HIV–	HIV+	Overall
Number of men	728	612	1340
Erectile dysfunction(ED), %(N)	16 (113)	21 (131)	18 (244)
Age (years)			
Median (IQR)	52 (45 – 59)	48 (42 – 54)	50 (43, 56)
Age (years), %(N)			
<40	16 (120)	20 (125)	18 (245)
40–44	10 (72)	17 (106)	14 (178)
45–49	17 (123)	24 (145)	20 (268)
50–54	19 (138)	19 (115)	19 (253)
≥55	38 (275)	20 (121)	30 (396)
Race, %(N)			
White	78 (567)	58 (354)	69 (921)
Black	13 (97)	26 (159)	19 (256)
Hispanic	9 (64)	16 (99)	12 (163)
Education (years), %(N)			
≤12	9 (68)	17 (101)	13 (169)
13–16	45 (325)	51 (313)	48 (638)
>16	46 (335)	32 (198)	40 (533)
History of Diabetes, %(N)	13 (97)	17 (101)	15 (198)
History of Hypertension, %(N)	73 (529)	69 (422)	71 (951)
Cumulative stimulant use years, Median (IQR)	0 (0, 0.573)	0.270(0, 2.578)	0 (0,1.226)
Cumulative cigarette smoking pack-years, Median (IQR)	0.030(0, 13.820)	2.670(0, 18.990)	0.525(0, 16.770)
Cumulative antihypertensive use-years, Median (IQR)	0 (0.0.434)	0 (0.0.314)	0 (0.0.388)
Cumulative antidepressant use-years, Median (IQR)	0 (0.1.016)	0.419(0.2.258)	0 (0, 1.606)

Table 2

Prevalence ratios (PR) for Erectile Dysfunction(ED) from multivariable models

	All men (N=1340)		HIV+ (N=612)		HIV- (N=728)	
	PR (95% CI)	p-value	PR (95% CI)	p-value	PR (95% CI)	p-value
HIV Status						
HIV+ (HIV- as reference group)	1.36 (1.06, 1.74) ^a	0.01	NA	NA	NA	NA
Age (years)(<40 as reference group)						
40-44	0.92 (0.55, 1.53)	0.74	0.78 (0.41, 1.50)	0.45	1.06(0.43, 2.58)	0.90
45-49	1.16 (0.75, 1.78)	0.51	0.99 (0.58, 1.72)	0.99	1.26(0.60,2.64)	0.54
50-54	1.28 (0.82, 1.98)	0.28	1.09 (0.62, 1.94)	0.75	1.43(0.68, 3.01)	0.35
≥ 55	1.60 (1.05, 2.43)	0.03	1.12 (0.62, 2.04)	0.70	2.13(1.08, 4.17)	0.03
Race(White as reference group)						
Black	1.48 (1.10, 2.00)	<0.01	1.32 (0.90, 1.94)	0.15	1.88(1.17, 3.01)	<0.01
Hispanic	1.21 (0.80, 1.85)	0.37	1.23 (0.73, 2.07)	0.43	1.10(0.49, 2.45)	0.83
BMI (1 unit)	1.00 (0.98, 1.03)	0.95	0.99 (0.96, 1.03)	0.82	1.01(0.98, 1.05)	0.40
Cumulative stimulant use (10 use-years)	1.03 (0.96, 1.11)	0.39	1.03 (0.96, 1.12)	0.41	1.01(0.86, 1.19)	0.90
Cumulative cigarette smoking (10 pack-years)	1.07 (1.01, 1.13)	0.02	1.07 (0.99, 1.15)	0.11	1.09(1.00, 1.18)	0.04
Cumulative antihypertensive (10 use-years)	1.93 (1.33, 2.79)	<0.01	2.36 (1.44, 3.89)	<0.01	1.60(0.92, 2.81)	0.10
Cumulative antidepressant (10 use-years)	1.59 (1.13, 2.22)	<0.01	1.88 (1.23, 2.87)	<0.01	1.04 (0.54, 2.01)	0.90
Cumulative HAART adherence years (10 years)	NA	NA	1.40 (0.89, 2.21)	0.15	NA	NA
CD4 ⁺ T-cell count (cells/ μ l) (>500 as reference group for HIV+)						
201-500	NA	NA	1.26 (0.89, 1.79)	0.19	NA	NA
≤ 200	NA	NA	1.38 (0.79, 2.40)	0.26	NA	NA

^aThis statistic compares HIV+ to HIV- men in the total sample, and shows higher ED prevalence among HIV+ men