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Sexual dysfunction in HIV-positive men is multi-factorial: A study of prevalence and associated factors

D. ASBOE[1], J. CATALAN[2], S. MANDALIA[1], N. DEDES[3], E. FLORENCE[4], W. SCHROOTEN[4], C. NOESTLINGER[4], & R. COLEBUNDERS[4]

[1]*Directorate of HIV/GU Medicine, Chelsea and Westminster Hospital, London, UK,* [2]*Psychological Medicine, South Kensington and Chelsea Mental Health Centre, London, UK,* [3]*Synthesis, Athens, Greece, and* [4]*Institute of Tropical Medicine, Department of Clinical Sciences, Antwerp, Belgium*

Abstract

To establish the prevalence of sexual dysfunction amongst HIV-positive men and to determine the factors associated with dysfunction we conducted a cross-sectional study in seven European HIV treatment centres. Data on medical history, antiretroviral treatment and laboratory results were collected by interview and case record review. Sexual function was evaluated by the participant self-completion of a questionnaire based on the International Index of Erectile Function (IIEF) 711/929. Seventy-seven percent of participants returned the questionnaire. Data from 668 (72%) respondents were included. Thirty-three percent (95%CI: 29.4–36.5%) had moderate/severe erectile dysfunction (EDF) and 24% (95%CI: 20.9–27.3%) had moderate to severe impairment of sexual desire. Variables significantly associated with EDF in multivariable analysis were older age (greater than 40 years), heterosexual status, non-alcohol drinking status, depression, antidepressants, psychotropic medications and duration of ARV therapy. Low sexual desire (LSD) was associated with older age (greater than 40 years), depression and black African ethnicity. We establish that EDF and LSD are common in both ARV naïve and ARV experienced, HIV-positive individuals. Erectile dysfunction was associated with long duration of ARV treatment, with a significantly increased risk of dysfunction in the quartile with the longest period of exposure. No significant association was seen with specific classes of anti-retrovirals. Older age, and depression were the variables most consistently associated with both EDF and LSD.

Introduction

Since the introduction of highly active antiretroviral therapy (HAART) there have been numerous reports of increased EDF in men. In these studies, prevalence rates of dysfunction of up to 70% have been described and in some the dysfunction has been linked with antiretroviral treatment (ARV), particularly protease inhibitors (PIs) (Collazos et al., 2002; Colson et al., 2002; Lallemand et al., 2002; Martinez et al., 1999; Schrooten et al., 2001; Sollima et al., 2001).

However, proving a link between this unwanted outcome and ARV treatment is problematic. First, HIV infection may be associated with sexual dysfunction. There are several reports of sexual dysfunction that predate the introduction of HAART (Catalan et al., 1992a, 1992b) and conditions commonly seen within the HIV context such as depression, peripheral neuropathy and hypogonadism are associated with sexual dysfunction in other settings. Secondly, establishing associations with particular drugs or classes of drugs is difficult, as these agents are used in combinations. Furthermore some of the ARV-associated toxicities, for example mitochondrial toxicities such as peripheral neuropathy can cause effects that persist. This could lead to the adverse effect being attributed wrongly to the treatments being taken at the time of assessment rather than to the treatment responsible.

In assessing the prevalence of sexual dysfunction in different groups, comparison of rates across different studies may also be misleading. Even when using the same assessment tool (IIEF) (Rosen et al., 1997) rates in different studies can vary markedly. For example the prevalence of moderate or severe EDF reported in a general Austrian population (Madersbacher et al., 2003) was as low as 5.8% while it was as high as 28% in a Singaporean study (Tan et al., 2003). It is likely that such differences are caused by factors such as age, co-morbidities and prescribed medications. In the studies in HIV-positive men, factors such as these

Correspondence: David Asboe, Chelsea and Westminster Hospital, 369 Fulham Road, London, SW10 9NH, UK. Tel: +44 (208) 846 6131. Fax +44 (208) 846 6198. E-mail: david.asboe@chelwest.nhs.uk

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have, in general, been poorly controlled for, hence we believe the confidence with which conclusions can be drawn from these studies is weakened.

The primary objectives of this study therefore are to establish the prevalence of EDF and LSD in both ARV naïve and experienced HIV-positive men attending HIV outpatient centres across Europe and to define the variables associated with sexual dysfunction. Due to the large number of variables that are potentially contributors to dysfunction, a large amount of data relating to these variables was collected. This not only included data relating to current HIV treatments but also previous treatments. Significant factors identified in univariate analysis were then examined further in a multivariable analysis.

Methods

Between April 2000 and May 2002 HIV-positive men attending one of seven European HIV treatment centres for routine HIV care were invited to join the study (the centres are those that were participants within the Eurosupport network and each centre obtained local ethics committee approval). If consent was given, two study components were administered. The study team completed the first part, which was a standardised data collection proforma that examined aspects of the medical history, antiretroviral treatment and laboratory results (total and fractionated cholesterol, triglycerides, testosterone, prolactin, lutenising hormone, follicle stimulating hormone and serum glucose). A large number of clinical data variables were examined in order to explore many possible associations.

The second part was a questionnaire (available in one of seven languages, English, French, German, Spanish, Italian, Dutch or Swedish) and was given to the participant to complete at home. This included questions assessing sexual function and other symptoms. Individuals were then asked to return this anonymous response by post to the coordinating centre. A code was used to link this to the data collected by the physician.

Sexual function was assessed within the questionnaire by questions based on the IIEF (Rosen et al., 1997). We adapted the questionnaire given to homosexual men (MSM) by including questions assessing erectile and other sexual functions related to oro-genital and both insertive and receptive anogenital sex. This questionnaire was piloted amongst MSM prior to the study.

Categories of sexual function assessed were erectile function, sexual desire, orgasmic function, intercourse satisfaction and overall satisfaction. Based on these scores, each aspect of sexual function was categorised as normal or as mild, moderate or severe EDF. The analysis presented relates to the outcomes moderate to severe EDF and moderate to severe impairment of sexual desire. Univariate logistic regression analysis was used to identify risk factors associated with these outcomes. Variables found to be significant ($p < 0.15$) were used to build multivariable models in order to identify significant risk factors. Those variables co-correlated with other variables were left in the model to adjust for residual confounding. Due to the interaction between different ARV variables, different multivariable models were run examining the effect on the model of each of those ARV factors found to be significant in univariate analysis. The model presented includes ARV duration, as this was the strongest association seen. The multivariable model presents significant independent predictors after adjusting for other variables in the model. All p values presented are 2-tailed. To preserve degrees of freedom we examined CD4 counts categorised into groups using median and interquartile ranges with a separate category for missing data.

To examine links between sexual dysfunction and ARV combinations, individuals were categorised as either ARV naïve, ARV experienced but PI naïve, PI experienced and currently taking PI or PI experienced but not currently taking a drug from this class. Categories relating to the number of PIs, nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors both currently and previously received were also examined. In order to negate the confounding of previous treatments on current treatment, a subanalysis of those on their first line ARV only was also performed.

As there was no consensus case definition for lipodystrophy at the time of study design, this was simply defined as having at one or more of the following symptoms confirmed by clinical examination: increase in abdominal girth, decrease of fat in the face and prominence of leg veins. Medications for psychiatric disorders assessed included antidepressants and other psychotropics (sedatives and major tranquillisers).

Results

Of the 929 individuals who consented for the study, 711 (77%) returned the questionnaire. Non-responders were more likely than responders to have an AIDS diagnosis (26.6% versus 20.5%; $p = 0.005$) and to ever have had diagnosed psychiatric disease (5% versus 1.8%; $p = 0.033$). Responders were more likely to be using methadone (5.9% versus 1.4%; $p = 0.005$). There were no significant differences between responders and non-responders in reported co-morbidities or usage of sildenafil, testosterone,

antidepressants or other psychotropic medication. Forty-four responses were excluded due to invalid or incomplete data. The overall response rate was 71.9%. In all, 486 of the participants were MSM and 182 heterosexual men, 552 were ARV experienced and 116 ARV naïve. Two hundred and twenty (32.9%; 95%CI: 29.4–36.5%) were categorised as having moderate/severe EDF and 161 (24.1%; 95%CI: 20.9–27.3%) moderate/severe LSD.

Erectile dysfunction

Overall, 35% of ARV experienced participants reported moderate or severe EDF compared with 22% of those who were ARV naïve. The factors associated with EDF in univariate analysis are shown in Table I. When a multivariable model was run with treatment experienced versus naïve as the ARV associated variable this association was not found to be significant (OR ARV naïve 0.69; 0.39–1.22; $p = 0.201$). However, examining duration of ARV use we found that the most experienced group (greater than 81 months on treatment) were significantly more likely than the other groups of ARV experienced and naïve participants to report EDF (Figure 1). We also performed models to examine whether there was an association between EDF and duration of exposure to either NRTIs or to PIs. In neither of these multivariable analyses was a significant association seen.

Low sexual desire

Overall 26% of ARV participants reported moderate to severe reduction in sexual desire compared with 13% of those who were ARV naïve. While this difference was significant in univariate analysis this was not the case when we used this as the ARV variable in multivariable analysis (OR ARV naïve 0.63; 0.32–1.21; $p = 0.166$). We did not demonstrate an association between LSD and any ARV related variable (see Figure 2).

When we analysed those individuals on their first line therapy only ($n = 86$) the variables significantly associated with EDF were older age, heterosexual status, smoking status, reported fatigue, pain in bones and joints and pins and needles in hands and feet. Being on a protease inhibitor containing combination was not associated with EDF.

As a supplement to the study we asked participants reporting EDF whether they had used therapies to treat this condition. The most frequent reported therapy was sildenafil, used by 112 individuals (16%). Smaller numbers reported using testosterone, growth hormone, yohimbine, alprostadil and papaverine. Twenty-six individuals reported they had changed their ARV combination and 26 reported they had stopped their ARV drugs in an attempt to improve sexual function. Within these two groups twenty-two individuals (42%) reported either manoeuvre to have been successful.

Discussion

While in univariate analysis ARV-experienced participants were significantly more likely than ARV-naïve individuals to experience EDF, when the data were adjusted in multivariable analysis we were unable to demonstrate a significantly higher prevalence of dysfunction in this group. In running several models, the only treatment-related variable associated with a significantly increased prevalence of dysfunction was in the quartile of patients with the longest duration of ARV treatment (greater than 81 months) where the relative risk of moderate/severe EDF was approximately three times that seen in ARV naïve individuals. Increased rates of dysfunction were not seen in individuals with less exposure to ARVs compared to treatment naïve individuals.

Most studies of EDF in people with HIV infection done since the introduction of HAART have looked only at individuals taking ARV treatment and so direct comparison with ARV naïve groups has not been possible. In the one study (Collazos et al., 2002) that did look at both groups, sexual dysfunction was seen in many more of the ARV treated individuals. However in this study the method of assessment was not well described nor were factors such as age controlled for.

We found no assciation between EDF and either categorical exposure or duration of exposure to specific classes of NRTI or PI therapy. While several studies have demonstrated an association with PIs (Collazos et al., 2002; Colson et al., 2002; Martinez et al., 1999; Schrooten et al., 2001) it is interesting that neither of the two groups that utilised the IIEF found a link with a particular class of medications (Lallemand et al., 2002; Sollima et al., 2001).

That EDF was associated with duration of ARV exposure, allied with the fact that both NRTIs and PIs are associated with toxicities that might be related to cumulative exposure (for example metabolic and mitochondrial toxicities) raises the possibility that sexual dysfunction may in some way be related to these toxicities. For example EDF has been seen in association with peripheral neuropathy and is also hypothesised to be associated with endothelial dysfunction seen in forms of metabolic syndrome (Esposito et al., 2005; Fonseca & Jawa, 2005). We were not, however, able to demonstrate a link with clinical manifestations of such toxicities except for the single association of reported tingling in the extremities (indicative of peripheral neuropathy) and LSD. Lallemand et al. (2002) also

Table I. Univariate logistic regression model showing likelihood of: Moderate/severe self reported EDF and Moderate/severe impairment of sexual desire.

Variable	Total (668)	EDF n (%) ($n=220$)	Odds Ratio	95% CI	Wald statistics p-value	LSD n (%) (n=161)	OR	95% CI	Wald statistics p-value
Age (years)									
Missing	11	4 (33.4)	0.59	(0.16–2.09)	0.411	2 (18.2)	0.39	(0.08–1.86)	0.235
< =35	173	39 (22.5)	0.30	(0.18–0.48)	0.000	27 (15.6)	0.32	(0.19–0.55)	<0.001
36–40	170	39 (22.9)	0.31	(0.19–0.49)	0.000	31 (18.2)	0.39	(0.23–0.65)	<0.001
41–46	166	65 (39.2)	0.66	(0.42–1.04)	0.070	47 (28.3)	0.69	(0.43–1.11)	0.122
>46	148	73 (49.3)	1			54 (36.5)	1		
Sexual orientation									
heterosexual	182	80 (44.0)	1.94	(1.36–2.76)	0.001	49 (26.9)	1.23	(0.83–1.82)	0.297
homosexual	486	140 (28.8)	1			112 (23.1)	1		
Ethnicity									
Other	38	11 (29.0)	0.84	(0.41–1.73)	0.634	8 (21.1)	0.86	(0.38–1.91)	0.805
Black African	15	8 (53.3)	2.35	(0.84–6.58)	0.103	7 (46.7)	2.81	(1.00–7.88)	0.050
White	615	201 (32.7)	1			146 (23.7)	1		
CDC stage									
Unknown	21	7 (33.3)	0.65	(0.25–1.72)	0.387	8 (38.1)	1.30	(0.50–3.35)	0.590
CDC A	348	95 (27.3)	0.49	(0.33–0.74)	0.001	71 (20.4)	0.54	(0.35–0.84)	0.006
CDC B	156	56 (35.9)	0.73	(0.46–1.16)	0.188	36 (23.1)	0.63	(0.38–1.06)	0.079
CDC C	143	62 (43.4)	1			46 (32.2)	1		
Duration HIV (months)									
Unavailable	11	1 (9.1)	0.25	(0.03–2.04)	0.198	1 (9.1)	0.35	(0.04–2.85)	0.328
>142	164	69 (42.1)	1.85	(1.17–2.93)	0.009	47 (28.7)	1.42	(0.86–2.34)	0.173
88–142	166	61 (36.8)	1.48	(0.93–2.35)	0.100	46 (27.7)	1.35	(0.82–2.24)	0.239
45–87	164	43 (26.2)	0.90	(0.56–1.47)	0.684	31 (18.9)	0.82	(0.48–1.41)	0.476
<45	163	46 (28.2)	1			36 (22.1)	1		
Treatment: exp v naïve									
Naive	116	26 (22.4)	0.53	(0.33–0.85)	0.009	16 (13.8)	0.45	(0.26 – 0.79)	0.005
Experienced	552	194 (35.1)	1			145 (26.3)	1		
Smoker									
No	190	52 (27.4)	0.70	(0.48–1.01)	0.054	40 (21.1)	0.79	(0.52–1.18)	0.246
Yes	478	168 (35.2)	1			121 (25.3)	1		
Alcohol drinker									
No	198	77 (38.9)	1.46	(1.03–2.06)	0.034	53 (26.8)	1.23	(0.84–1.79)	0.296
Yes	470	143 (30.4)	1			108 (23.0)	1		
Recreational drug taker									
No	513	166 (32.4)	0.89	(0.61–1.31)	0.565	120 (23.4)	0.85	(0.56–1.28)	0.435
Yes	155	54 (34.8)	1			41 (26.5)	1		

Table I (*Continued*)

Variable	Total (668)	EDF n (%) ($n=220$)	Odds Ratio	95% CI	Wald statistics p-value	LSD n (%) (n = 161)	OR	95% CI	Wald statistics p-value
Co Morbidities									
Diabetes									
No	648	212 (32.7)	0.73	(0.29–1.81)	0.496	156 (24.1)	0.95	(0.34–2.66)	0.924
Yes	20	8 (40.0)	1			5 (25.0)	1		
Hypertension									
No	642	207 (32.2)	0.48	(0.22–1.04)	0.064	155 (24.1)	1.06	(0.42–2.69)	0.901
Yes	26	13 (50.0)	1			6 (23.1)	1		
Peripheral neuropathy									
No	643	205 (31.9)	0.31	(0.14–0.71)	0.005	148 (23.0)	0.28	(0.12–0.62)	0.002
Yes	25	15 (60.0)	1			13 (52.0)	1		
Psychiatric disease									
No	640	207 (32.3)	0.55	(0.26–1.18)	0.125	148 (23.1)	0.35	(0.16–0.75)	0.007
Yes	28	13 (46.4)	1			13 (46.4)	1		
Body shape changes									
Increased abdominal girth									
Yes	107	43 (40.2)	1.46	(0.95–2.23)	0.083	37 (34.6)	1.86	(1.19–2.91)	0.006
No	561	177 (31.6)	1			124 (22.1)	1		
Decreased fat in face									
Yes	134	47 (35.1)	1.13	(0.76–1.68)	0.556	41 (30.6)	1.52	(1.00–2.31)	0.050
No	534	173 (32.4)	1			120 (22.5)	1		
Prominence of leg veins									
Yes	83	34 (41.0)	1.49	(0.93–2.38)	0.098	33 (39.8)	2.36	(1.46–3.81)	<0.001
No	585	186 (31.8)	1			128 (21.9)	1		
Symptoms in previous 4 weeks									
Fatigue									
No/blank	290	73 (25.2)	0.53	(0.38–0.74)	0.001	47 (16.2)	0.45	(0.31–0.66)	<0.001
Yes	378	147 (38.9)	1			114 (30.2)	1		
Depression									
No/blank	455	127 (27.9)	0.50	(0.36–0.70)	0.001	80 (17.6)	0.35	(0.24–0.50)	<0.001
Yes	213	93 (43.7)	1			81 (38.0)	1		
Anxiety									
No/blank	454	135 (29.7)	0.64	(0.46–0.90)	0.011	92 (20.3)	0.53	(0.37–0.77)	<0.001
Yes	214	85 (39.7)	1			69 (32.2)	1		
Pins/needles in hands/feet									
No/blank	492	137 (27.9)	0.43	(0.30–0.62)	0.001	93 (18.9)	0.37	(0.25–0.54)	<0.001
Yes	176	83 (47.2)	1			68 (38.6)	1		

Table I (*Continued*)

Variable	Total (668)	EDF n (%) ($n=220$)	Odds Ratio	95% CI	Wald statistics p-value	LSD n (%) (n = 161)	OR	95% CI	Wald statistics p-value
Relationship problems									
Don't know	147	62 (42.2)	1.32	(0.88–1.99)	0.185	41 (27.9)	1.07	(0.68–1.67)	0.779
No	243	59 (24.3)	0.58	(0.40–0.85)	0.005	46 (18.9)	0.64	(0.42–0.98)	0.038
Yes	278	99 (35.6)	1			74 (26.6)	1		
Laboratory values									
CD4 count									
Unavailable	4	0 (0.00)	–	–	–	1 (25.0)	1.51	(0.15–15.03)	0.725
<333	166	64 (38.6)	1.91	(1.19–3.06)	0.007	47 (28.3)	1.79	(1.06–3.01)	0.028
333–498	166	64 (38.6)	1.91	(1.19–3.06)	0.007	40 (24.1)	1.44	(0.85–2.45)	0.180
499–709	166	51 (30.7)	1.35	(0.83–2.19)	0.221	43 (25.9)	1.58	(0.94–2.68)	0.086
≥710	166	41 (24.7)	1			30 (18.1)	1		
Viral load									
Unavailable	6	1 (16.7)	0.41	(0.05–3.50)	0.411	3 (50.0)	3.13	(0.62–15.72)	0.166
$>10^5$	38	12 (31.6)	0.93	(0.46–1.90)	0.852	9 (23.7)	0.97	(0.45–2.11)	0.942
10^4–10^5	79	24 (30.4)	0.88	(0.53–1.48)	0.639	16 (20.3)	0.80	(0.44–1.43)	0.444
10^3–10^4	70	26 (37.1)	1.20	(0.71–2.02)	0.499	18 (25.7)	1.08	(0.61–1.93)	0.785
$<10^3$	475	157 (33.1)	1			115 (24.2)	1		
Blood glucose									
Unavailable	43	13 (30.2)	0.88	(0.42–1.82)	0.721	14 (32.6)	1.92	(0.91–4.05)	0.089
<4.8	162	50 (30.9)	0.90	(0.56–1.45)	0.668	41 (25.3)	1.34	(0.79–2.28)	0.273
4.8–5.0	41	16 (39.0)	1.29	(0.63–2.63)	0.480	12 (29.3)	1.64	(0.75–3.58)	0.213
5.1–5.9	268	90 (33.6)	1.02	(0.67–1.56)	0.922	63 (23.5)	1.22	(0.75–1.98)	0.423
≥5.9	154	51 (33.1)	1			31 (20.1)	1		
Total cholesterol									
Unavailable	13	3 (23.1)	0.60	(0.16–2.27)	0.456	5 (38.5)	1.90	(0.59–6.07)	0.279
<4.3	156	55 (35.3)	1.10	(0.71–1.70)	0.679	29 (18.6)	0.69	(0.41–1.16)	0.164
4.3–4.9	105	36 (34.3)	1.05	(0.64–1.73)	0.844	27 (25.7)	1.05	(0.61–1.81)	0.854
5.0–5.9	192	59 (30.7)	0.89	(0.58–1.37)	0.604	50 (26.0)	1.07	(0.68–1.69)	0.769
≥6	202	67 (33.2)	1			50 (24.8)	1		
HDL cholesterol									
Unavailable	171	50 (29.2)	0.59	(0.38–0.90)	0.013	42 (24.6)	0.98	(0.62–1.56)	0.940
0–1.3	272	77 (28.3)	0.56	(0.39–0.81)	0.002	63 (23.2)	0.91	(0.60–1.38)	0.653
> =1.4	225	93 (41.3)	1			56 (24.9)	1		
Trigylcerides									
Unavailable	31	9 (29.0)	0.77	(0.33–1.78)	0.540	8 (25.8)	1.03	(0.43–2.47)	0.952
<1.1	166	45 (27.1)	0.70	(0.44–1.11)	0.133	33 (19.9)	0.73	(0.44–1.23)	0.236
1.1–1.9	132	51 (38.6)	1.18	(0.74–1.90)	0.482	37 (28.0)	1.15	(0.69–1.92)	0.593
2.0–2.9	169	56 (33.1)	0.93	(0.59–1.46)	0.482	40 (23.7)	0.92	(0.56–1.50)	0.728
≥3.0	170	59 (34.7)	1			43 (25.3)	1		

Table I (*Continued*)

Variable	Total (668)	EDF n (%) ($n=220$)	Odds Ratio	95% CI	Wald statistics p-value	LSD n (%) (n = 161)	OR	95% CI	Wald statistics p-value
Testosterone									
Unavailable	345	112 (32.5)	0.83	(0.52–1.35)	0.457	73 (21.2)	0.62	(0.37–1.04)	0.071
<14	74	29 (39.2)	1.12	(0.60–2.10)	0.728	17 (23.0)	0.69	(0.34–1.39)	0.303
14–17	67	22 (32.8)	0.85	(0.44–1.64)	0.626	23 (34.3)	1.21	(0.62–2.37)	0.572
18–23	89	23 (25.8)	0.60	(0.32–1.14)	0.121	20 (22.5)	0.67	(0.35–1.31)	0.244
≥24	93	34 (36.6)	1			28 (30.1)	1		
Medications									
Total duration of ARV (months)									
Naive	118	26 (22.0)	0.26	(0.15–0.45)	<0.001	17 (14.4)	0.32	(0.17–0.59)	<0.001
≤43	137	42 (30.7)	0.41	(0.25–0.66)	<0.001	34 (24.8)	0.62	(0.37–1.04)	0.072
44–62	138	40 (29.0)	0.37	(0.23–0.61)	<0.001	31 (22.5)	0.54	(0.32–0.92)	0.024
63–81	137	40 (29.2)	0.38	(0.23–0.62)	<0.001	31 (22.6)	0.55	(0.32–0.93)	0.027
>81	138	72 (52.2)	1			48 (34.8)	1		
^Cumulative duration on NRTI (months)									
Naive	118	26 (22.0)	0.34	(0.20–0.59)	<0.001	17 (14.4)	0.32	(0.17–0.60)	<0.001
≤82	137	39 (28.5)	0.48	(0.29–0.79)	0.004	34 (24.8)	0.63	(0.37–1.07)	0.086
83–123	138	51 (37.0)	0.71	(0.44–1.15)	0.163	39 (28.3)	0.75	(0.45–1.26)	0.280
124–160	138	42 (30.4)	0.53	(0.32–0.87)	0.012	24 (17.4)	0.40	(0.23–0.71)	0.002
>160	137	62 (45.3)	1			47 (34.3)	1		
^Cumulative duration on PI (months)									
Naïve	118	26 (22.0)	0.42	(0.24–0.74)	0.003	17 (14.4)	0.43	(0.22–0.83)	0.012
No PI	93	25 (26.9)	0.54	(0.30–0.98)	0.043	18 (19.4)	0.62	(0.32–1.19)	0.147
≤26	115	36 (31.3)	0.67	(0.39–1.16)	0.154	30 (26.1)	0.90	(0.50–1.62)	0.736
27–41	112	37 (33.0)	0.73	(0.42–1.26)	0.255	24 (21.4)	0.70	(0.38–1.28)	0.249
42–57	116	50 (43.1)	1.12	(0.66–1.89)	0.672	40 (34.5)	1.35	(0.77–2.36)	0.295
>57	114	46 (40.4)	1			32 (28.1)	1		
Current no. PI									
Naïve	118	26 (22.0)	0.63	(0.38–1.03)	0.063	17 (14.4)	0.54	(0.30–0.95)	0.033
≥2	64	24 (37.5)	1.33	(0.76–2.32)	0.321	24 (37.5)	1.91	(1.08–3.37)	0.025
1	168	71 (42.3)	1.62	(1.10–2.39)	0.015	44 (26.2)	1.13	(0.74–1.74)	0.578
0	318	99 (31.1)	1			76 (23.9)	1		
Current no. NNRTI									
Naïve	118	26 (22.0)	0.63	(0.38–1.05)	0.075	17 (14.4)	0.50	(0.28–0.88)	0.017
0	258	104 (39.6)	1.52	(1.07–2.15)	0.020	70 (27.1)	1.10	(0.75–1.60)	0.634
1	292	90 (30.8)	1			74 (25.3)	1		

Table I (*Continued*)

Variable	Total (668)	EDF n (%) ($n=220$)	Odds Ratio	95% CI	Wald statistics p-value	LSD n (%) (n = 161)	OR	95% CI	Wald statistics p-value
Experienced–number of different NRTIs pre current therapy									
Naïve	118	26 (22.0)	0.71	(0.38–1.34)	0.295	17 (14.4)	0.70	(0.34–1.47)	0.349
≥4	198	87 (43.9)	1.98	(1.15–3.39)	0.014	66 (33.3)	2.09	(1.14–3.83)	0.017
3	99	42 (42.4)	1.86	(1.01–3.42)	0.047	30 (30.3)	1.82	(0.92–3.59)	0.086
2	162	39 (24.1)	0.80	(0.44–1.44)	0.454	31 (19.1)	0.99	(0.51–1.91)	0.972
1	3	1 (33.3)	1.26	(0.11–4.52)	0.853	0 (0.0)	unstable	–	–
currently on 1st line	88	25 (28.4)	1			17 (19.3)	1		
Experienced–number of different PI's pre current therapy									
Naïve	118	2 (22.0)	0.72	(0.41–1.28)	0.269	17 (14.4)	0.67	(0.34–1.29)	0.230
≥3	135	68 (50.4)	2.60	(1.58–4.29)	0.000	49 (36.3)	2.26	(1.31–3.89)	0.003
1–2	276	8731.5)	1.18	(0.75–1.85)	0.469	67 (24.3)	1.27	(0.77–2.09)	0.345
currently on 1st line	139	40 (28.1)	1.00			28 (20.1)	1		
Other medications									
Antidepressants									
Yes	51	24 (47.1)	1.91	(1.07–3.39)	0.028	21 (41.2)	2.38	(1.32–4.30)	0.004
No	617	196 (31.8)	1			140 (22.7)	1		
Psychotropics	37	24 (64.9)	4.10	(2.04–8.22)	<0.001	20 (54.1)	4.09	(2.09–8.01)	<0.001
Yes	631	196 (31.1)	1			141 (22.4)	1		
No									
Sildenafil									
Yes	108	48 (44.4)	1.80	(1.19–2.75)	0.006	36 (33.3)	1.74	(1.11–2.72)	0.015
No	560	172 (30.7)	1			125 (22.3)	1		
Testosterone therapy									
Yes	32	18 (56.3)	2.76	(1.35–5.66)	0.006	11 (34.4)	1.70	(0.80–3.60)	0.168
No	636	202 (31.8)	1			150 (23.6)	1		
Alprostadil									
Yes	23	14 (60.9)	3.31	(1.41–7.78)	0.006	8 (34.8)	1.72	(0.71–4.12)	0.228
No	645	206 (31.9)	1			153 (23.7)	1		
Anti-hypertensives									
Yes	25	15 (60.0)	3.20	(1.42–7.26)	0.005	7 (28.0)	1.23	(0.51–3.01)	0.643
No	643	205 (31.9)	1			154 (24.0)	1		
Fibrates/statins									
Yes	37	19 (51.4)	2.26	(1.16–4.40)	0.017	12 (32.4)	1.55	(0.76–3.17)	0.226
No	631	201 (32.1)	1			149 (23.6)	1		

^If no of NRTI or no of PI (unboosted) >1 then cumulative duration on drug is multiplied by no of same class ARV drugs.
Data for insomnia, pain in joints, LDL cholesterol, ischaemic heart disease, methadone not shown.

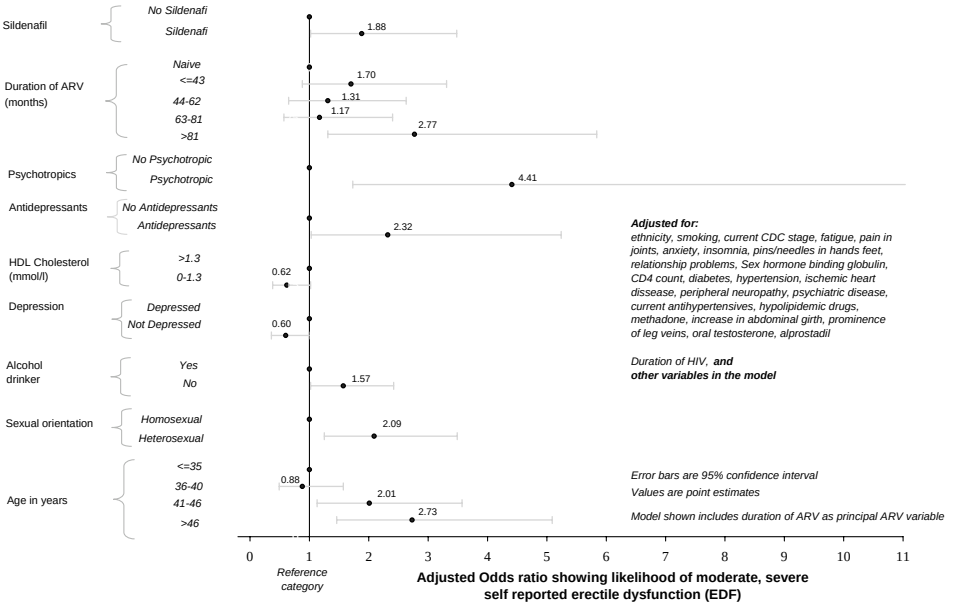

Figure 1. Multivariable logistic regression model showing likelihood of moderate/severe erectile dysfunction with model containing duration ARV as principal ARV category.

reported the absence of an association between EDF and lipodystrophy.

Older age was the variable most strongly associated with both EDF and LSD aspects of decreased sexual function. The risk of moderate to severe EDF for an individual in the oldest quartile was almost three times that for someone in the youngest quartile. Studies of EDF in the general population consistently demonstrate older age as one of the variables most strongly associated with dysfunction.

There was an association between anti-depressants and other psychotropic medication and EDF. Although anti-depressants, psychotropic medications, anti-hypertensives and statins have all been previously linked to sexual dysfunction (Bruckert et al., 1996; Rizvi et al., 2002) it remains problematic proving causality particularly when underlying conditions such as depression may be exerting an influence (Araujo et al., 1998). In the Massachusettts male aging study, the apparent associations between medications and sexual dysfunction mostly disappeared when adjustment for co-morbidities and health behaviours was made (Derby et al., 2001). While we enquired broadly about relationship problems we did not explore some other issues that might have had influence. Previously factors such as

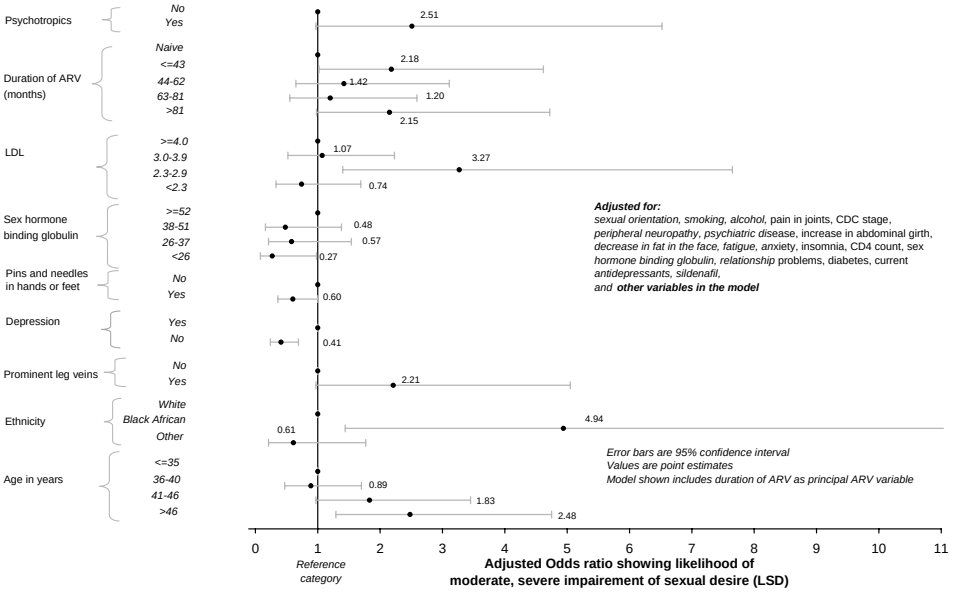

Figure 2. Multivariable logistic regression model showing likelihood of moderate/severe impairment of sexual desire with model containing duration ARV as principal ARV category.

discordant HIV status, disclosure status and the type and nature of sexual relationships have been postulated to affect sexual function.

Most participants who switched or stopped ARV medications due to EDF came off PI based regimens. While a percentage of these individuals reported improvement, it is not necessarily correct to conclude from this that the ARV agents were responsible for the dysfunction.

The prevalence of moderate/severe LSD was lower than that of EDF. No ARV associated variable that we tested was associated with LSD in multivariable analysis.

There are limitations to the study. The participation of centres and subjects from different countries presented many challenges. While guided by study protocols and proformas, there may have been differences in the way in which individuals were recruited and how data was collected. Although the study recruitment protocol was inclusive and non-selective it is possible that there was a bias in patient selection and that therefore the study group is not representative of the entire clinic population. While the MSM adapted questionnaire was piloted it was not formally validated. It is possible that some of the increased risk of sexual dysfunction seen in heterosexual men relates to assessment of dysfunction rather than any inherent difference. Lastly, the large number of variables examined increases the possibility of finding a spurious association by chance and also the possibility that a positive association was lost by the dilutional effect of including so many variables.

We have demonstrated a high prevalence of sexual dysfunction in both ARV treatment naïve and experienced individuals. Sexual dysfunction is associated with older age, depression and longer duration of ARV. We were not able to demonstrate an association between EDF and a particular class of ARV or with specific HIV or drug-related toxicities. That sexual dysfunction is multi-factorial is an important finding. For those affected it is often a major concern and leads to considerable diminution in quality of life. There is also evidence that the attribution of sexual dysfunction to PI is contributing to lower levels of adherence over time (Trotta et al., 2003). In these circumstances it remains important to discuss with patients the uncertainty over this association and to assess, investigate and treat this condition appropriately. Meanwhile further, preferably prospective, study is required so that any relationship with ARV or related conditions can be further defined.

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