Antiviral Therapy 2013; **18:**337–344 (doi: 10.3851/IMP2372)

Original article

The prevalence of erectile dysfunction and its association with antiretroviral therapy in HIV-infected men: the Swiss HIV Cohort Study

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Background: Here, we aimed to determine the prevalence of erectile dysfunction (ED) among HIV-infected men and its association with components of antiretroviral therapy.
Methods: Cross-sectional data on sexual dysfunction were collected in the Swiss HIV Cohort Study (SHCS) between December 2009 and November 2010. Multilevel logistic regression models were used to estimate the association between ED and exposure to 24 different antiretroviral drugs from four drug classes.
Results: During the study period, 5,194 of 5,539 eligible men in the SHCS had a follow-up visit; 4,064 men answered a question on ED for the first time. Among these men, ED was experienced often by 459 (11%), sometimes by 543 (13%), rarely by 389 (10%), never by 2,526 (62%) and 147 (4%) did not know. ED was associated with older age, an earlier HIV diagnosis and depression. No association was found with any drug class; however, ED was associated with cumulative exposure to either zalcitabine (OR 1.29 per year of use; 95% CI 1.07, 1.55) or enfuvirtide (OR 1.28; 95% CI 1.08, 1.52).
Conclusions: Around 1 in 10 men in the SHCS reported often experiencing ED. We found no association between ED and any drug class, but those exposed to zalcitabine or enfurvitide (drugs no longer or rarely used) were more likely to report ED; this second association was probably not causal.

Introduction

Erectile dysfunction (ED) is an increasingly recognized condition in HIV-infected men, with significant impact on quality of life and satisfaction with sexual life and partnership [1]. ED is more prevalent in men with HIV than in age-matched men without HIV [2]; however, the reported prevalence among men with HIV varies widely from 9% to 74% [3–12].

The pathophysiology of ED is complex and includes neurological, vascular, endocrinological, psychiatric and psychosocial disorders as well as pharmacological effects. Many of the disorders and risk factors known to be associated with ED are over-represented in HIV-infected men [13], in particular polyneuropathy, arterial hypertension, dyslipidaemia, central obesity, abnormal body mass index (BMI), diabetes mellitus, hypogonadism, depression, as well as smoking, alcohol and drug abuse [1,14].

ED was a common complication of HIV before the era of antiretroviral therapy (ART), due to hypogonadism associated with advanced HIV disease [15].

Both ED and hypogonadism continue to occur at higher rates in patients receiving ART, despite a significant improvement in prognosis [7,8,16]. It is still not certain whether ART has an effect on ED. While some studies suggest ART, particularly protease inhibitors (PIs), is associated with ED [3–6,12,17], other studies fail to show any association [7–9,11,18]. Researchers have speculated that an association with PIs could arise because of indinavir induced neuropathy [4], or because of the effect of PIs (particularly ritonavir) on sex hormone metabolism [6], or indirectly because of concomitant treatment with antihypertensive or lipid-lowering drugs [19]. If neuropathy was the cause of this association, then ED might also be associated with the nucleoside reverse transcriptase inhibitor drug class, since a number of drugs in this class (such as stavudine, didanosine and zalcitabine) are thought to cause peripheral neuropathy. Most studies are small and inadequately controlled for potential confounders, such as diabetes, dyslipidaemia and central obesity – conditions exacerbated by ART and known to be associated with ED [1]. Thus, any association of ART with ED may be entirely mediated via worsening risk factors for ED rather than because the drugs themselves have additional independent effects. In addition, when estimating the effect of different drugs, typically only some of the drugs in use are selected for regression modelling; however, the drugs excluded can also affect model estimates. More reliable estimates of drug effects require both a regression model that includes all drugs in use and a model for the correlation between the effects of the different drugs [20].

We estimated the prevalence of ED among men in the Swiss HIV Cohort Study (SHCS) using a question on ED introduced into routine follow-up. In particular, we assessed associations between ED and either past or current exposure to a full range of antiretroviral drugs and drug classes.

Methods

Study population

The SHCS is a multicentre prospective cohort study with continuing enrolment of HIV-infected adults (aged ≥18 years) [21]. Enrolment in the SHCS is independent of the stage of disease, the degree of immunosuppression or whether the individual is receiving ART. Over 15,000 HIV-infected individuals have been included in the SHCS so far, corresponding to approximately 45% of all those ever testing positive for HIV in Switzerland. Informed consent is obtained from all participants. Participants are followed-up every 6 months at outpatient clinics and private practices and asked to provide information on sociodemographics, comorbidities and concomitant medications. Laboratory data, including $CD4^+$ T-cell counts and HIV viral load, are collected at each visit.

In December 2009, a question on the frequency of ED during the previous 6 months ('often', 'sometimes', 'rarely', 'never' or 'don't know') was introduced into a questionnaire used as part of routine follow-up. The question was taken from the 15-item International Index of Erectile Dysfunction (IIEF-15) questionnaire, a validated instrument for the assessment of sexual dysfunction [22,23]. The questionnaire was administered by a clinician or study nurse at the outpatient clinic or private practice.

Our cross-sectional study included all HIV-infected men in the SHCS who answered this question on ED for the first time during a regular follow-up visit between 1 December 2009 and 30 November 2010, whether currently on ART or not.

Statistical analyses

Our primary outcome was men who reported 'often' experiencing ED in the previous 6 months. A logistical regression model was used to estimate associations between this outcome and cumulative exposure (in years) to each of the antiretroviral drugs ever used by those in our study population. There were 24 different drugs used from four classes: eight nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs), four non-nucleoside reverse transcriptase inhibitors (NNRTIs), nine PIs and three drugs (maraviroc, raltegravir and enfuvirtide) from other drug classes – these infrequently used drugs were grouped into a heterogeneous class named 'other'.

With few outcomes relative to the large number of antiretroviral drugs in use, conventional logistic regression models can lead to unreliable estimates [24]. We therefore fit a hierarchical (multilevel) model where the first level includes individual drugs, and the second level provides a model for the correlation between the effects of different drugs [20]. Given drugs from the same class may have similar effects on ED, the drug class provides a useful prior model so that unreliable estimates of the effect of exposure to a particular drug 'shrink' towards the drug class mean. Each drug was allowed to have a residual effect beyond the effect of its drug class and we assumed independent residual effects that were normally distributed with mean 0 and variance σ^2. The degree of 'shrinkage' depends on the amount of information in the data and on the residual variance σ^2 [25]; as the value of σ^2 increases, there is less 'shrinkage' and parameter estimates approach those of the conventional model [26]. We considered it unlikely that ORs for individual drug effects would be below 0.50 or above 2.0; therefore, residual effects beyond the class mean should also lie well within this range. Simulation suggests that it is better to overestimate than underestimate when

assigning a value for σ^2 [25], and while we assumed a residual variance of 1/8 to reflect our prior opinion that the residual effects for these drugs should lie within the range 0.5–2.0, we considered other values in additional analyses. Although the 'other' class was included to improve the reliability of estimates for individual drugs in this group, the overall estimate for the 'other' drug class has no clinical meaning.

We adjusted for those potential confounding risk factors thought to be associated with both exposure and outcome but not on a causal pathway between exposure and outcome [27]: age, BMI before starting ART, time since HIV diagnosis, non-Caucasian ethnicity, daily alcohol consumption ≥40 g (more than moderate daily alcohol intake for men based on the WHO guidelines [28,29]), depression (where a patient reports either suffering from depression, a diagnosis of depression or treatment with antidepressant drugs), diabetes before starting ART (defined as a clinical diagnosis, a random plasma glucose >11.1 mmol/l, taking antidiabetic drugs or insulin), current intravenous drug use (IDU) and IDU as the likely mode of transmission. Earlier studies have shown that both age and BMI are strongly associated with the prevalence of ED [3,10–12,18]. Hence age and BMI before starting ART were represented in our models by a linear spline, with knots at 40 and 60 for age and at 20 and 25 for BMI [30]; using a linear spline should provide better covariate adjustment for these covariates. For the 1,016 patients who started ART before SHCS registration, we used the first available BMI measurement; for the 316 patients with a missing date of HIV diagnosis, we used the SHCS registration date to calculate an approximate time since HIV diagnosis.

The nature of any association between an outcome and a drug or drug class was assessed by an OR and its 95% CI; an OR greater than one indicates that ED is more likely in patients exposed to an individual drug or drug class than in unexposed patients. In Additional file 2, we describe how to fit this model in SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA).

Additional analyses

We addressed uncertainty about the residual variance σ^2 by reporting estimates assuming other values (1/24 and ∞). A value of 1/24 represents a 95% prior opinion that ORs for residual effects lie within a narrower range of 0.67–1.5; a value of infinity corresponds to a conventional logistic regression model.

We also considered the effect of current use of these drugs on ED. Current exposure variables take values of one or zero, depending on whether a specific drug was currently in use or not, respectively. Because of co-linearity between current and cumulative exposure, we did not include both sets of exposure variables in the same model but fit separate models. We used the same covariates in the current exposure model, except variables such as BMI and diabetes were assessed at the most recent follow-up rather than before starting ART.

As a secondary outcome, we combined response categories 'never' and 'don't know' and then modelled ED as a four-category ordinal variable, ordered by frequency from 'never' to 'often'. We fit a hierarchical proportional odds model to this ordered outcome, so that the OR reflects the association between a 1-year increase in the cumulative exposure to a drug and more frequently reported ED.

Finally we considered a number of alternative covariates: we replaced time since HIV diagnosis by duration of untreated HIV; we replaced current IDU either by current smoking status or by the square root of the number of cigarettes smoked per day; in the current exposure model, we added hypertension (or use of an antihypertensive drug) at the most recent follow-up.

Results

Patient characteristics

On 1 December 2009, 5,539 HIV-infected men were registered and still participating in the SHCS. Of these, 5,194 (94%) had at least one follow-up visit in the year between 1 December 2009 and 30 November 2010, and 4,064 (73%) completed the question on ED at their first visit during this period. Those without a follow-up visit were on average younger with less exposure to PIs, and less likely to be Caucasian, homosexual or in a stable relationship (Table 1). However, they were more likely to be smokers, report past or current IDU and have detectable viraemia and lower $CD4^+$ T-cell counts. Compared with those answering the question on ED, those with no answer were less likely to be Caucasian or to report current IDU.

Of the 4,064 who answered, ED was experienced 'often' by 459 (11%) men during the 6 months prior to their follow-up visit, 'sometimes' by 543 (13%), 'rarely' by 389 (10%), 'never' by 2,526 (62%) and 147 (4%) 'didn't know'. Those 'often' experiencing ED were on average older, had been infected with HIV for longer, had started antiretroviral therapy earlier, had greater exposure to PIs and were more likely to be Caucasian, have depression, receive psychiatric treatment, report body fat loss or gain, and have hypertension or diabetes (Table 1).

In our hierarchical model for the primary outcome, ED was more likely to occur in older patients, in those with an earlier HIV diagnosis and in those with depression or diabetes (Additional file 2).

Associations between erectile dysfunction and antiretroviral drugs

Of the 4,064 who answered the question on ED, 3,760 (93%) were currently on ART. The most commonly

Table 1. Characteristics of 5,539 HIV-infected men in the SHCS when first answering a question on ED between 1 December 2009 and 30 November 2010

Characteristic	'Often' experienced ED[a]		No answer[d]	No follow-up[e,f]
	Yes[b]	No[c]		
Median age, years (IQR)	53 (46–60)	46 (40–52)	47 (41–54)	44 (38–50)
Caucasian ethnicity, %	94	90	87	81
Median BMI, kg/m^2 (IQR)	24 (22–27)	24 (22–26)	24 (22–26)	24 (22–26)
Body fat loss, %	32	16	20	16
Body fat gain, %	27	16	16	17
Arterial hypertension, %[g]	50	38	37	30
Diabetes mellitus, %	13	5	9	6
Smoker, %	47	45	42	55
Alcohol consumption ≥40 g/day, %	7	7	6	8
Homosexual, %	51	52	48	40
Stable relationship, %	54	60	53	48
Depression, %	27	13	15	17
HIV transmission via IDU, %	16	14	14	21
Current IDU, %	20	23	16	25
Median time since HIV diagnosis, years (IQR)[h]	13.9 (8.2–19.5)	9.5 (4.5–15.6)	11.0 (5.4–16.6)	9.0 (4.3–14.9)
Viral load >50 copies/ml, %	34	22	26	40
Median CD4$^+$ T-cell count, cells/µl (IQR)	535 (349–718)	535 (393–708)	509 (359–666)	469 (313–639)
Previous AIDS (CDC stage C), %	34	22	26	22
Median time since ART initiation, years (IQR)	12.1 (6.5–14.3)	7.6 (2.5–12.9)	9.0 (3.0–13.3)	7.2 (1.5–12.8)
Median cumulative time on PI, years (IQR)	4.6 (1.0–9.7)	2.3 (0–6.7)	2.8 (0–7.3)	1.2 (0–4.7)

[a]A total of 4,064 (73%) participants answered question on erectile dysfunction (ED). [b]*n*=459 (11%). [c]*n*=3,605 (89%). [d]*n*=1,130 (21%). [e]*n*=345 (6%). [f]Data from the most recent follow-up prior to the study period. [g]Systolic blood pressure ≥140 mmHg (≥135 mmHg in diabetic patients) or diastolic blood pressure ≥90 mmHg (≥85 mmHg in diabetic patients) or currently on an antihypertensive drug. [h]From date of first positive HIV test to date of study visit (or 1 December 2009 if no follow-up during the study period). Of the 4,064 men answering the question on ED, a documented date of a first positive test was available for 3,006, a reported date of a first positive test was available for 742, and the date of the registration visit was used to calculate an approximated time since diagnosis for the remaining 316. ART, antiretroviral treatment; BMI, body mass index; CDC, Centers for Disease Control and Prevention; IDU, intravenous drug use; PI, protease inhibitor; SHCS, Swiss HIV Cohort Study.

used NRTIs were lamivudine and tenofovir, used by 3,036 (75%) and 2,727 (67%) men, respectively (Figure 1); the most commonly used NNRTI and PI were efavirenz (53%) and lopinavir (37%), respectively; and the most commonly used drug from another drug class was raltegravir (6%).

Having adjusted for covariates, ED was not associated with cumulative exposure to any of the drug classes (Figure 2). However, some individual antiretroviral drugs may have an appreciable association with ED: zalcitabine, among NRTIs, and enfuvirtide, among the new drugs, were both associated with ED (OR 1.29, 95% CI 1.07, 1.55 and OR 1.28, 95% CI 1.08, 1.52, respectively). Both lamivudine and abacavir were weakly associated with ED; none of the PIs had an association with ED.

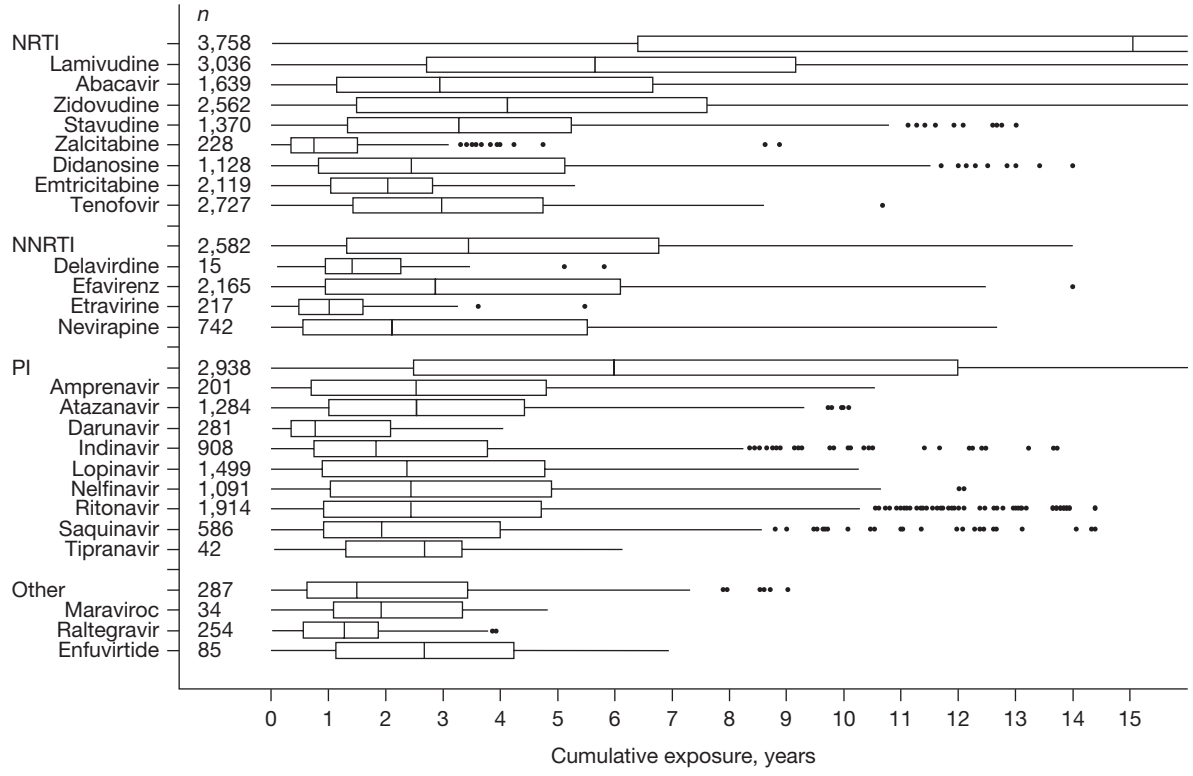
Different values of the residual variance σ^2 gave similar estimates of associations between ED and the various drugs except for maraviroc, a drug not used by many patients in this study (Additional file 2). With maraviroc, estimates in the conventional model ($\sigma^2=\infty$) were 'shrunk' towards the 'other' drug class mean in the two hierarchical models.

In the current exposure analysis, there were appreciable associations between ED and both abacavir (OR 1.32, 95% CI 0.99, 1.76) and raltegravir (OR 1.68, 95% CI 1.16, 2.44); these were associations not seen in the cumulative exposure analysis (Additional file 2). However, the association between ED and enfuvirtide seen in the cumulative exposure analysis was weaker in the current exposure analysis (OR 1.20 95% CI 0.49, 2.94). With ED as a four-category ordinal variable, estimates were similar except for a slightly weaker association between ED and zalcitabine (OR 1.13, 95% CI 0.97, 1.32). Replacing covariates with alternatives (replacing time since HIV diagnosis with duration of untreated HIV, or current IDU with current smoking behaviour) or adding hypertension to the current exposure model had no material effect on estimates of associations between ED and exposure to the various drugs or drug classes (data not shown).

Discussion

In this cross-sectional analysis of the SHCS, 11% and 13% of HIV-infected men reported 'often' and 'sometimes' experiencing ED in the past 6 months, and this indicates a substantial rate of sexual dysfunction. In contrast to other studies, we found no association between ED and the cumulative use of common antiretroviral drugs.

Figure 1. Cumulative exposure to components of ART for 4,064 men in the SHCS first answering a question on ED between 1 December 2009 and 30 November 2010



For each drug and drug class, the box shows the IQR, with a bar at the median; the continuous line extends 1.5× the IQR below the lower quartile and above the upper quartile; outside that range, individual points are shown. ART, antiretroviral therapy; ED, erectile dysfunction; *n*, the number of patients exposed to that particular drug or drug class; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside or nucleotide reverse transcriptase inhibitor; other, other new drug classes; PI, protease inhibitor; SHCS, Swiss HIV Cohort Study.

In previous studies, the reported prevalence of ED has varied from 9% to 74%. This wide range in prevalence may be due to the lack of standardized, validated methods for its assessment and differences between the various populations studied. Of note, the studies reporting the highest prevalence all allowed patients to complete anonymous questionnaires [7,9,11,12]. In the SHCS the question on ED was asked at an interview during a consultation and therefore it is highly likely that we have underestimated its prevalence.

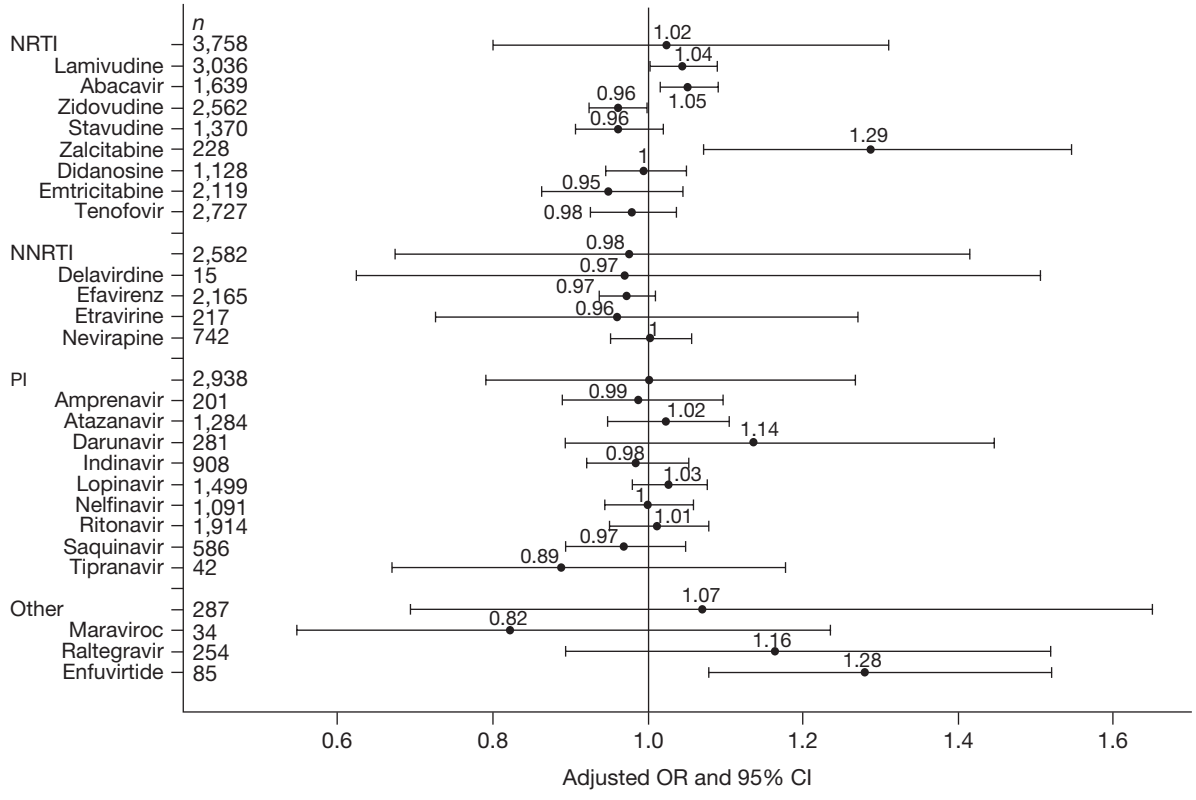
The large number of patients included in this study and the appreciable prevalence of ED allow us to investigate associations between ED and a full range of individual antiretroviral drugs. Since ED could be caused by cumulative exposure to a drug, through vascular or neurological damage, or by current exposure, were it to interfere directly with the physiological processes of arousal and erection, we analysed these two types of exposure separately. Statistically significant associations were seen with cumulative exposure for the NRTIs lamivudine and abacavir; however, these were weak associations, with ORs between 1.0 and 1.1, of little clinical significance and such associations may merely reflect residual confounding. Most importantly, we could not confirm an association between ED and PIs as a class, nor between ED and any individual PI. This information should reassure HIV care providers and their patients. Patient adherence to PIs may improve if they do not attribute ED to this particular drug class [31]. Previous reports of an association between ED and PIs are conflicting, possibly due to differences in statistical methods used for analysis and in the variables used for confounder control. Several studies have reported an increased risk of ED with PIs as a drug class [3,5,12], or with individuals PIs, in particular indinavir [4] and ritonavir [6]. Another larger cross-sectional study found no association between ED and cumulative exposure to either NRTIs or PIs [10].

We found an association between ED and cumulative exposure to both zalcitabine and enfuvirtide, drugs

that are now no longer or very rarely used. Zalcitabine is associated with a high risk of distal sensory neuropathy, in particular in conjunction with diabetes or low BMI [32,33]; peripheral neuropathy is associated with ED [34]. The associations seen here between ED and cumulative exposure to enfuvirtide and current exposure to raltegravir are probably not causal but reflect confounding with poor health. Following the introduction of raltegravir in Switzerland 2007, most patients using enfuvirtide in the form of subcutaneous injection were switched to raltegravir [35]. The association between ED and current but not cumulative exposure to raltegravir most likely reflects this switching practice in patients with advanced HIV infection who have experienced virological failure on multiple regimens. Residual confounding is also the most likely reason for the association seen between ED and the current exposure to abacavir, despite adjusting for the most recent values of variables, such as BMI and diabetes, in the current exposure model. In the SHCS, patients receiving zidovudine and stavudine were frequently switched to abacavir because of lipoatrophy, peripheral neuropathy or dyslipidaemia, known side effects of these drugs [36]. Typically these patients had a high risk of cardiovascular disease and were more frequently prescribed cardiovascular drugs known to cause ED such as beta-blockers. Unfortunately the SHCS database does not have complete information on concomitant drug use.

ED has a complex pathophysiology involving vascular, neurological, endocrinological and psychiatric disorders and psychosocial factors, and many of these disorders increase with age. Consistent with previous studies [3,10–12], ED was strongly associated with older age in our study. We found a strong association between ED and depression, reflecting the important role of psychiatric and psychosocial factors in sexual health and function. Several factors might explain the observed association between ED and time since HIV diagnosis. Longer

Figure 2. Associations between reports of 'often' experiencing ED and cumulative exposure to components of ART



OR (95% CI) per year of exposure to each antiretroviral class and individual drug (n=4,064) are shown. The model was adjusted for age (linear spline), ethnicity, body mass index before starting antiretroviral therapy (ART; linear spline), diabetes mellitus before starting ART, depression, daily alcohol consumption, current intravenous drug use, intravenous drug use as the likely mode of transmission and time since HIV diagnosis. ED, erectile dysfunction; *n*, the number of patients exposed to that particular drug or drug class; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside or nucleotide reverse transcriptase inhibitor; other, other new drug classes; PI, protease inhibitor.

periods of continued viral replication lead to chronic inflammation; this may promote endothelial inflammation and as a consequence atherosclerosis, known to be associated with ED [37]. An earlier HIV diagnosis is also associated with AIDS-related chronic conditions such as lipodystrophy, metabolic syndrome, hepatic diseases and cardiovascular diseases; all most likely associated with a higher risk of ED. Patients with an earlier HIV diagnosis may also suffer from chronic fatigue, another factor associated with ED.

Our study has several strengths. Results are based on a large sample of patients from a fairly representative population of HIV-infected men. We carried out a sophisticated analysis that allowed us comprehensively address associations between ED and individual antiretroviral drugs. Our estimates are relatively precise, particularly for individual PIs (other than darunavir and tipranavir). Our estimates are largely unchanged if ED is represented by a set of ordered categories rather than by a more arbitrary binary outcome ('often' experiencing ED). The SHCS database allowed us to control for important confounders not considered in some other studies, such as depression, diabetes and alcohol consumption, although the associations between ED and these confounders are not the focus of this study.

The following limitations should be kept in mind. We were not able to use a full validated questionnaire (such as the IIEF-15) in routine follow-up, and the use of only a single question from this questionnaire to assess ED must limit the validity of our results. The question refers to a period of 6 months prior to the interview, and so in the current exposure analysis we may incorrectly attribute ED during the past 6 months to the drugs in current use. Some misclassification bias is possible given that 13% of patients changed ART in the 6 months prior to the interview. However, consistent estimates for most antiretroviral drugs in current and cumulative exposure analyses, along with logical difference between analyses for other drugs, suggests that misclassification bias has not had material consequences. However, we are likely to have underestimated the prevalence of ED for two reasons: first, the assessment of ED by clinicians or nurses during regular follow-up is prone to underreporting because patients are less likely to disclose sexual dysfunction in face-to-face questioning than in an anonymous questionnaire; second, 27% of all eligible patients had no follow-up during the study period but had baseline characteristics that suggest that these patients might be at higher risk of ED. The association with age may be an overestimate if younger men are less likely to report ED. The SHCS does not routinely collect hormonal parameters, in particular testosterone. We were therefore not able to adjust for such factors, known to be associated with ED, or to further explore hormonal mechanisms of ED in relevant patient groups. Finally, our analysis used cross-sectional data and we were not able to exclude men who had ED before exposure to ART; therefore, no causal conclusions can be reached.

In conclusion, approximately 1 in 10 men in the SHCS reported often experiencing ED. Because of the high prevalence and the important impact of ED on quality of life, HIV care givers should regularly ask about ED. Doing so may identify factors related to ED that are amenable to treatment or intervention. We found no association between ED and any drug class; in particular, there was no association between ED and any of the PIs used in our cohort. Longitudinal studies are needed to definitively rule out any causal effect of ART on ED.

Acknowledgements

This study has been financed within the framework of the SHCS, supported by the Swiss National Science Foundation (grant number 33CS30_134277). The Basel Institute for Clinical Epidemiology and Biostatistics is supported by grants from Santésuisse and from the Gottfried and Julia Bangerter-Rhyner-Foundation. EB, MC, PV, BH, RW, HF and MS were responsible for data collection in their respective hospitals. HCB, JY and CF designed this study. QW and JY carried out the statistical analyses. QW wrote the first draft of the manuscript and created the graphs. JY, HF, HCB and CF revised the manuscript. All authors reviewed, commented on and approved the final version of the manuscript.

Disclosure statement

EB has been consultant for BMS, Gilead, ViiV Healthcare, Pfizer, MSD and Janssen. He has received unrestricted research grants from Gilead, Abbott, Roche and MSD. He also received travel grants from Abbott, Gilead, ViiV Healthcare, MSD and Janssen. MC has received unrestricted research grant from Gilead and MSD. He has received travel grants from Boehringer–Ingelheim, BMS, Gilead and MSD. His institution has received advisory board honorarium from BMS, Gilead, MSD, Janssen–Cilag and ViiV. The institutions of HF and HCB have received payments for participation in advisory boards and/or unrestricted educational grants and/or travel grants from Abbott, BMS, ViiV Healthcare, Roche, Gilead, MSD, Boehringer–Ingelheim, Tibotec–Janssen and unrestricted research support from Gilead, MSD and Roche. All other authors declare no competing interests.

Additional files

Additional file 1: A list of the members of the SHCS can be found via http://www.intmedpress.com/uploads/documents/AVT-12-OA-2644_Wang_Add_file1.pdf

Additional file 2: Further information on model fitting in SAS and the results of sensitivity analyses can be found via http://www.intmedpress.com/uploads/documents/AVT-12-OA-2644_Wang_Add_file2.pdf

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Accepted 25 August 2012; published online 12 September 2012