BRIEF REPORT

Evaluation of HIV Protease Inhibitor Use and the Risk of Sudden Death or Nonhemorrhagic Stroke

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Concerns have arisen about possible effects of protease inhibitors (PIs) on cardiac conductivity. We found no significant association between current or recent PI exposure and sudden death or nonhemorrhagic stroke (adjusted rate ratio, 1.22; 95% confidence interval, .95–1.57), whereas cumulative exposure to PIs was associated with an increased risk (adjusted rate ratio, 1.06 per year of exposure; 95% confidence interval, 1.01–1.11).

Concerns have arisen about protease inhibitors (PIs) and their potential adverse effects on cardiac conductivity, as manifested through prolongation of QT and PR interval durations on the standard electrocardiogram (ECG) [1]. These concerns are largely based on case reports and small single-center studies [2, 3]. Over the last 2 years, the Food and Drug Administration has issued warnings that ritonavir-boosted lopinavir and ritonavir-boosted saquinavir may cause prolongation of QTc and PR intervals [4]. Recently, investigators from the Strategies for Management of Antiretroviral Therapy (SMART) Study Group reported that several PI-based regimens (whether or not boosted with ritonavir) were associated with prolongation of the PR interval, and average QT interval was significantly reduced among those receiving boosted PIs compared with those receiving nonnucleoside reverse-transcriptase inhibitors (NNRTIs) [5].

Prolongation of the PR interval could be an early manifestation of an ongoing conduction defect that may lead to complete AV block. Although rarely seen without other cardiac abnormalities, one possible clinical manifestation of severe PR interval prolongation may be congestive heart failure. Although the associations may not be causal, it has been suggested that prolonged PR interval may be not only a marker of AV conduction but also a predictor of atrial fibrillation [6] and mortality [7]. Prolongation or shortening of the QTc interval, which reflects issues with repolarization of myocardial cells, predisposes the heart for torsade de pointes arrhythmia or ventricular fibrillation with its clinical manifestation of sudden death.

The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, a large observational multicohort collaboration of human immunodeficiency virus (HIV)–positive individuals, has previously reported an association between cumulative exposure to the PI drug class and an increased risk of myocardial infarction [8]. Ischemic coronary disease and some drugs used to treat this and other related conditions may lead to abnormal cardiac conductivity; sudden death due to ventricular fibrillation is a known complication of myocardial infarction.

Sudden death and nonhemorrhagic strokes may be rare "end-stage" outcomes of different ECG abnormalities, for example, prolonged QT or PR intervals. If exposure to PIs does, indeed, cause these ECG abnormalities directly, we may expect to see an excess risk of sudden death and nonhemorrhagic stroke in patients currently or recently exposed to PIs. The aim of this study was to describe associations between current or recent exposure to the PI drug class and the risk of sudden death or nonhemorrhagic stroke in the D:A:D study.

METHODS

All incident cases of MI and all deaths (irrespective of cause) are reported to the D:A:D study coordinating office for validation [8, 9]. Centrally validated cases (with cardiologist input) of sudden deaths and nonhemorrhagic strokes were identified using standard case definitions [10].

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Owing to the rarity of sudden death [10], our main analyses considered associations between exposure to the PI class and the composite end point of sudden death or the first nonhemorrhagic stroke occurring during prospective follow-up. Hemorrhagic strokes or strokes of unknown cause were excluded from these analyses. Follow-up was considered from the date of D:A:D enrolment until the first of these events (if patients experienced both events, the date of the nonhemorrhagic stroke was taken as the end point); for patients not experiencing one of these events, follow-up was right-censored on the earliest of date of death from another cause, 1 February 2009, or 6 months after the last clinic visit.

We considered associations between the composite end point and cardiovascular disease (CVD) risk factors (age, sex, ethnicity, body mass index [BMI], smoking status, family and personal history of CVD, hypertension [systolic blood pressure $\geq$150 mm Hg, diastolic blood pressure $\geq$100 mm Hg, use of ACE inhibitors, and/or antihypertensive drugs], diabetes mellitus, use of lipid-lowering drugs, total cholesterol, high-density lipoprotein cholesterol, triglyceride levels), as well as HIV transmission group, calendar year, and participating cohort. Variables were categorized as in Table 1. Event rates were calculated as the number of events divided by the total person-years of follow-up (PYFU), and associations were described using Poisson regression (PROC GENMOD in SAS software, version 9.1). Reflecting our primary hypothesis that PIs may affect QT or PR intervals which could result in sudden death, associations were first considered with current or recent use of the PI class (any use of PI within the past year); this definition of exposure captures a relatively short-lived impact of the drugs on the outcome. To allow for the possibility of other biological mechanisms (see Introduction), secondary analyses incorporated cumulative exposure to PIs (ie, years of prior exposure). PI exposure was counted regardless of whether the PI had been boosted with ritonavir. Finally, we assessed associations with sudden deaths alone; owing to the small number of end points, adjustments were limited to age and previous CVD event.

RESULTS

Over the course of 234 818 PYFU, 250 of the 49 737 patients in the D:A:D study experienced one of the events (1.06/1000 PYFU; 95% confidence interval [CI], .93–1.20). There were 78 sudden deaths (0.33/1000 PYFU; 95% CI, .26–.41) and 172 nonhemorrhagic strokes (0.73/1000 PYFU; 95% CI, .62–.84). At the time of the event, patients experiencing either event were more likely to be male, to have a BMI $<$18 kg/m^2, to be smokers, to be receiving antihypertensive medication, to have diabetes, or to have been exposed to drugs from the NRTIs previous nucleoside reverse-transcriptase inhibitor (NRTI) compared with the remaining study population (Table 1). Patients experiencing either end points had a greater median exposure to PIs, NRTIs, and NNRTIs and had higher total cholesterol and triglyceride levels than the remaining study population, whereas CD4 counts were lower in those experiencing an event.

Established CVD risk factors associated with the composite end point were older age (adjusted rate ratio [RR] per year of age, 1.07; 95% CI, 1.06–1.08); BMI $<$18 kg/m^2 (2.76; 1.72–4.42), compared with BMIs of 18–26 kg/m^2; previous CVD (3.02; 2.08–4.37); current smoking (1.62; 1.13-2.32), compared with never smoking; diabetes mellitus (1.50; 1.05–2.15); and hypertension (1.60; 1.19–2.15). Calendar year and participating cohort were also associated with the composite end point, although there was no clear trend to an increasing or decreasing risk in later years. Use of lipid-lowering drugs was not associated with the composite end point (data not shown).

In total, 31 876 (64%) of the study group had received PIs with a median exposure by end of follow-up of 1.50 years (interquartile range, 0.00–4.82 years). Among patients currently or recently exposed to PIs, the event rate was 1.30/1000 PYFU (120 events/92 414 PYFU; 95% CI, 1.07–1.53), compared with 0.91/1000 PYFU (130 events/142 405 PYFU; 95% CI, .76–1.07) for those not recently exposed to PIs. In unadjusted analyses, those recently exposed to PIs were 42% more likely to experience an event (unadjusted RR, 1.42; 95% CI, 1.08–1.82; $P = .005$) than those not exposed to PIs. In an analysis that considered cumulative exposure to the PI class, rather than recent exposure, the RR was 1.10 per year of exposure (95% CI, 1.05–1.14; $P < .0001$).

After adjustment for CVD risk factors, calendar year, and cohort, the RR associated with recent PI exposure was attenuated (adjusted RR, 1.22; 95% CI, .95–1.57; $P = .12$); the RR for cumulative exposure was similarly attenuated (adjusted RR, 1.06; 95% CI, 1.01–1.11; $P = .01$). When both covariates were included in the model, the adjusted RR for current or recent PI exposure dropped further to 1.02 (95% CI, .75–1.40; $P = .89$), whereas that for cumulative exposure was unchanged (adjusted RR, 1.06; 1.00–1.12; $P = .05$). When the sudden deaths alone were analyzed, RRs were similar both before (current or recent exposure, 1.46 [95% CI, .94–2.28; $P = .09$]; cumulative exposure, 1.08 [95% CI, 1.00–1.15; $P = .04$]) and after (current or recent exposure, 1.33 [95% CI, .85–2.08; $P = .21$]; cumulative exposure, 1.03 [95% CI, .96–1.11; $P = .40$]) adjustment for confounders.

DISCUSSION

We did not observe an independent association between current or recent use of PIs (as a class) and the risk of sudden death or nonhemorrhagic stroke. Although our primary hypothesis was that any association with PI exposure would be relatively short lived, we did find that the risk of an event increased as cumulative exposure increased; this association remained

Table 1. Demographic, Cardiovascular, and HIV Characteristics of Patients in D:A:D study at Last Date of Follow-up

Variable	Composite End Point (n = 250)	Sudden Death (n = 78)	Nonhemorrhagic Stroke (n = 172)	D:A:D Population With No Event at Last Follow-up (n = 49 487)
Age, median (IQR), year	53 (45–60)	49 (42–59)	53 (47–61)	43 (37–50)
Male sex	213 (85.2)	66 (84.6)	147 (85.5)	36 339 (73.4)
Ethnicity				
White	128 (51.2)	46 (59.0)	82 (47.7)	24 945 (50.4)
Black	26 (10.4)	6 (7.7)	20 (11.6)	4828 (9.8)
Other	2 (0.8)	…	2 (1.2)	1392 (2.8)
Unknown	94 (37.6)	26 (33.3)	68 (39.5)	18 322 (37.0)
BMI				
<18 kg/m^2	21 (8.4)	4 (5.1)	17 (9.9)	1887 (3.8)
18–26 kg/m^2	164 (65.6)	45 (57.7)	119 (69.2)	30 446 (61.5)
26–30 kg/m^2	30 (12.0)	12 (15.4)	18 (10.5)	7140 (14.4)
>30 kg/m^2	17 (6.8)	5 (6.4)	12 (7.0)	3023 (6.1)
Unknown	18 (7.2)	12 (15.4)	6 (3.5)	6991 (14.1)
Mode of infection				
Homosexual	126 (50.4)	41 (52.6)	85 (49.4)	21 540 (43.5)
Heterosexual	47 (18.8)	21 (26.9)	26 (15.1)	7542 (15.2)
IDU	54 (21.6)	11 (14.1)	43 (25.0)	15 976 (32.3)
Other or unknown	23 (9.2)	5 (6.4)	18 (10.5)	4429 (9.0)
Smoking status				
Current smoker	85 (34.0)	26 (33.8)	59 (34.3)	12 722 (25.7)
Former smoker	153 (61.2)	50 (65.0)	103 (59.9)	26 678 (53.9)
Family history of CVD				
Yes	16 (6.4)	4 (5.2)	12 (7.0)	3179 (6.4)
No	153 (61.2)	41 (53.3)	112 (65.1)	29 411 (59.4)
Unknown	81 (32.4)	32 (41.6)	48 (27.9)	16 879 (34.1)
Previous CVD event	77 (30.8)	52 (66.7)	25 (14.5)	1248 (2.5)
Diabetes mellitus	35 (14.0)	6 (7.7)	29 (16.9)	2324 (4.7)
Hypertension	86 (34.4)	18 (23.1)	68 (39.5)	7246 (14.6)
Receipt of lipid-lowering drugs	22 (8.8)	5 (8.5)	17 (9.9)	2257 (4.6)
Coinfected with hepatitis C virus	46 (18.4)	20 (25.6)	26 (15.1)	9145 (18.)
Currently or recently exposed to ART				
PIs	116 (46.4)	35 (44.9)	81 (47.1)	18 529 (37.4)
NNRTIs	86 (34.4)	27(34.6)	59 (34.3)	17 406 (35.2)
NRTIs	204 (81.6)	57 (73.1)	147 (85.5)	35 170 (71.2)
Ever exposed to ART				
PIs	208 (83.2)	67 (85.9)	141 (82.0)	31 660 (64.0)
NNRTIs	159 (63.6)	50 (64.1)	109 (63.4)	29 240 (59.1)
NRTI	240 (96.0)	75 (96.2)	165 (95.9)	41 323 (83.5)
Duration of previous exposure to ART, median (IQR), y				
PIs	2.9 (0.8–5.5)	2.6 (1.1–4.9)	3.0 (0.5–6.0)	1.3 (0.0–4.6)
NNRTIs	0.8 (0.0–2.8)	0.9 (0.0–2.8)	0.8 (0.0–2.9)	0.5 (0.0–3.3)
NRTIs	6.3 (3.0–9.0)	5.7 (3.4–7.9)	6.4 (2.8–9.5)	4.5 (0.9–9.2)
Log HIV-1 RNA, median (IQR), copies/mL	1.7 (1.7–3.1)	2.6 (1.7–4.1)	1.7 (1.7–3.0)	1.7 (1.7–3.1)
CD4 count, median (IQR), cells/mm^3	476 (320–664)	310 (197–539)	401 (212–615)	476 (320–644)
Lipids, median (IQR), mmol/L				
TG	2.1 (1.4–3.1)	2.1 (1.4–3.1)	2.1 (1.3–3.1)	1.5 (1.0–2.4)
TC	5.2 (4.1–6.2)	5.3 (4.1–6.2)	5.2 (4.2–6.1)	4.8 (4.1–5.6)
HDL-C	1.1 (0.9–1.4)	1.0 (0.9–1.4)	1.1 (0.9–1.4)	1.2 (0.9–1.5)

Unless otherwise indicated, data represent No. (%) of subjects.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CVD, cardiovascular disease; D:A:D, Data Collection on Adverse Events of Anti-HIV Drugs; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; IDU, injection drug use; IQR, interquartile range; NNRTIs, nonnucleoside-reverse transcriptase inhibitors; NRTIs, nucleoside reverse-transcriptase inhibitors; PIs, protease inhibitors; TC, total cholesterol; TG, triglycerides.

significant after adjustment for potential confounders and is more consistent with our previously reported results indicating that PI exposure may lead to the development of ischemic coronary disease [9], which, in turn, may result in sudden death.

Although we did not identify a significant association with current or recent exposure, only 250 events were observed (reflected in the wide CI for this association). Thus, our study is likely to be sufficiently powered to detect only a strong signal between current or recent exposure to the PI drug class and the end point. Furthermore, we do not have sufficient power to consider associations with specific PI drugs, in particular ritonavir-boosted lopinavir and ritonavir-boosted saquinavir, reports of which initially raised concerns with the Food and Drug Administration [4]. Of note, data from the SMART study suggest that associations with PIs may be class wide rather than limited to specific PIs [5].

Owing to the expected rarity of sudden deaths [10, 11] our primary analysis was based on a composite end point that also incorporated nonhemorrhagic strokes. This approach makes the assumption that any association with PI exposure is the same for the different components of the end point. The fact that several PIs have been reported to have an effect on the electric conductivity of the heart means that both outcomes are likely to be of relevance. However, because the underlying mechanisms that link ECG abnormalities to sudden deaths and nonhemorrhagic strokes may differ, the degree of association with sudden death, if any, may be different from the degree of association with nonhemorrhagic stroke. Our finding of a higher RR for the association of current or recent PI exposure with sudden deaths (1.33) than for the composite end point (1.22) is consistent with this possibility. If such an association exists, this may reflect antiretroviral drug-induced ECG abnormalities. If prolongation or shortening of the QTc interval develops, this reflects issues with repolarization of myocardial cells and may be caused by drugs that block the human ether-à-go-go–related gene (HERG) channels [12], which may either directly affect the HERG-channels or indirectly cause subclinical myocardial ischemia. Of interest, PIs have been shown to affect HERG directly [2, 13]. The blocking of HERG channels has been shown to be dose dependent for several PIs, and this suggests that PIs could predispose to torsade de pointes [2]. Unfortunately, information on ECG results is not collected routinely in the D:A:D study, and other nonfatal adverse effects of any ECG abnormalities are not captured. Furthermore, information on genetic predispositions that may cause prolongation of the QTc interval are also not available.

We identified several factors (older age, previous CVD, current smoking, diabetes, and hypertension) that were associated with an increased event rate, similar to findings in the general population [10]. Interestingly, we found that lower rather than higher BMI was associated with an increased risk of the end point; the HIV-positive population has a relatively low prevalence of obesity, and this contributes less to cardiovascular events than other CVD risk factors. Low BMI is strongly associated with many outcomes, possibly because it may identify a group of patients with more advanced disease or other comorbidities.

The study has limited information on concomitant cocaine or methadone use or on use of antiarrythmic drugs, which may have an impact on cardiac conductivity, although we have no reason to believe that use of these drugs will differ according to level of PI exposure. Finally, we are unable to distinguish sudden deaths that result from conduction disturbances caused by genetics from those that are secondary to ischemic heart disease.

To guide decisions regarding the routine use of ECG screening of all patients receiving PIs, future studies are required that consider the impact of individual PIs on the cardiac risk profile of individual patients. Although we included follow-up information on >49 000 patients, only 78 sudden deaths were identified, and CIs for this end point were wide. It is very unlikely that any other study of HIV-positive individuals with clinical end points will collect information on sufficient sudden deaths as an outcome. Although misclassification of sudden deaths cannot be excluded, use of the Coding of causes of Death (CoDe) system [14] and the evaluation of events in consultation with a cardiologist allow us to minimize this possibility.

In conclusion, we found no evidence for an increased risk of sudden death or nonhemorrhagic stroke among HIV-positive individuals with recent exposure to PIs, although cumulative exposure to PIs was associated with these outcomes. Further analyses are planned when more end points (through extended follow-up) have accrued.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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