

# Protease inhibitors and cardiac autonomic function in HIV-infected patients: a cross-sectional analysis from the Strategies for Management of Antiretroviral Therapy (SMART) Trial

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**To cite:** Soliman EZ, Roediger MP, Duprez DA, *et al*. Protease inhibitors and cardiac autonomic function in HIV-infected patients: a cross-sectional analysis from the Strategies for Management of Antiretroviral Therapy (SMART) Trial. *BMJ Open* 2013;**3**:e002523. doi:10.1136/bmjopen-2012-002523

► Prepublication history and additional material for this paper are available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2012-002523>).

Received 20 December 2012  
Revised 5 February 2013  
Accepted 6 February 2013

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## ABSTRACT

**Objective:** To compare cardiac autonomic function as measured by heart rate variability for HIV-infected participants taking protease inhibitors (PIs) with those taking a non-nucleoside reverse transcriptase inhibitor without a PI (NNRTI-no PI) regimen.

**Design:** Cross-sectional analysis.

**Setting:** Multicentre study.

**Participants:** 2998 participants (average age 44 years, 28% females) enrolled in the Strategies for Management of Antiretroviral Therapy (SMART) trial.

**Primary outcome measures:** Heart rate and two heart rate variability measures (the SD of all filtered RR intervals over the length of the recording (SDNN) and the root mean square of successive differences in normal RR intervals (rMSSD)).

**Results:** At study entry, 869 participants were taking a boosted PI (PI/r), 579 a non-boosted PI and 1550 an NNRTI-no PI. Median values (IQR) of heart rate, SDNN and rMSSD were: 68 (60–75) beats/min (bpm), 21 (13–33) ms, 22 (13–35) ms in the PI/r group, 68 (60–75) bpm, 21 (13–33) ms and 21 (14–33) ms in the non-boosted PI group and 69 (62–77) bpm, 20 (13–31) ms and 21(13–33) ms in the NNRTI-no PI group. After adjustment for baseline factors, for those given PI/r and non-boosted PI, heart rate was 2.2 and 2.8 bpm, respectively, lower than the NNRTI-no PI group ( $p < 0.001$  for both). On the other hand, compared with the NNRTI-no PI group, log SDNN and log rMSSD were significantly greater for those in the non-boosted PI ( $p$  values for baseline adjusted differences in log-transformed SDNN and rMSSD were 0.004 and 0.001) but not for those in the PI/r group at the 0.01  $\alpha$ -level.

**Conclusions:** Compared to an NNRTI-no PI regimen, heart rate was lower for those taking a PI/r or non-boosted PI and heart rate variability was greater, reflecting better cardiac autonomic function, for those taking a non-boosted PI regimen but not PI/r.

## ARTICLE SUMMARY

### Article focus

- Cardiac autonomic dysfunction manifested as reduced heart rate variability has been reported in HIV infection.
- The impact of protease inhibitors on cardiac autonomic function, considering their favourable effect on HIV suppression and the unfavourable diabetogenic and atherogenic effects, is unclear.

### Key messages

- Different protease inhibitors have a different impact on cardiac autonomic function as measured by heart rate variability.
- Compared to a regimen that does not include protease inhibitors, a non-boosted protease inhibitor regimen was associated with better heart rate variability.
- Compared to a regimen that does not include protease inhibitors, a boosted protease inhibitor regimen was not associated with better heart rate variability.

### Strengths and limitations of this study

- This is the largest study to extensively examine cardiac autonomic function as measured by heart rate variability in HIV-infected participants taking protease inhibitors.
- The limitations of this study include a lack of examining the prognostic significance of the differences in heart rate variability among protease inhibitors.

## INTRODUCTION

The introduction and wide use of combination antiretroviral therapy (ART) have made it possible to obtain long-term HIV viral suppression and increased CD4 T-cell counts. This has resulted in improved death rates in HIV-infected patients, but has also led to long-term concern about the possibly adverse

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effects of treatment including a greater risk of cardiovascular disease.<sup>1</sup> Adverse effects could be due to the drugs themselves, or they could be caused indirectly through the development of dyslipidaemia, insulin resistance and metabolic syndrome, well known to be associated with ART.<sup>2-3</sup> Protease inhibitors (PIs), in particular, have been linked to both hypercholesterolaemia and development of insulin resistance,<sup>2-5</sup> and can subsequently negatively influence the cardiovascular system, including cardiac autonomic function. Nevertheless, the overall impact of PIs on cardiac autonomic function, considering their favourable effect on HIV suppression and the unfavourable diabetogenic and atherogenic effects, is unclear.

Heart rate variability is a non-invasive and easy to obtain ECG measure of cardiac autonomic nervous system function.<sup>6-7</sup> Cardiac autonomic dysfunction manifested as reduced heart rate variability and increased resting heart rate has been reported in HIV infection,<sup>8-10</sup> and has been demonstrated to severely debilitate HIV-infected patients, namely by postural hypotension and syncope as well as possible life-threatening cardiac arrest.<sup>11-13</sup> Nevertheless, several of these studies were conducted before the wide use of highly active ART.

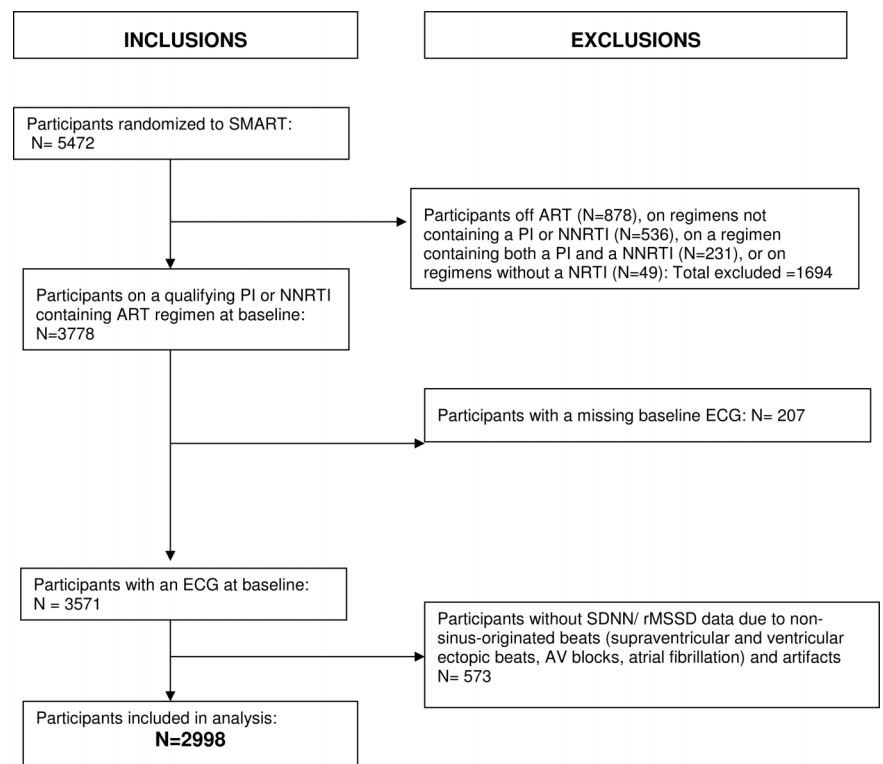
The purpose of this cross-sectional analysis was to compare heart rate and cardiac autonomic function as measured by heart rate variability for HIV-infected participants taking PI-based regimens (boosted and non-boosted) with those taking a non-nucleoside reverse transcriptase inhibitors without a PI (NNRTI-no PI) regimen in the Strategies for Management of Antiretroviral Therapy (SMART) trial.

## METHODS

### Study population

SMART is an open-label randomised trial comparing two ART strategies. The study was approved by the institutional review board of all participants' sites. Detailed descriptions of the design and aims of the study have been published elsewhere.<sup>14-15</sup> Briefly, individuals infected with HIV, who were older than 13 years and were not pregnant or breastfeeding, were eligible for inclusion in the SMART study if their CD4 T-cell count exceeded 350 cells/mm<sup>3</sup> and they were willing to participate. At baseline, an ART and medical history were obtained, CD4 T-cell count and plasma HIV RNA levels were measured and a 12-lead ECG was obtained. This analysis only utilised data from the baseline visit. All the SMART trial participants (N=5472) were considered eligible for the present analysis, except those who were off ART, on an ART regimen not containing a PI and/or an NNRTI at baseline, on a regimen containing both a PI and an NNRTI or on an ART regimen not containing a nucleoside reverse transcriptase inhibitor (NRTI) or those who were missing their baseline ECG or were with ECG conditions that interfere with appropriate measurement of heart rate variability. After these exclusions, 2998 participants remained and were included in this analysis (figure 1). Baseline characteristics comparing participants with the SD of all filtered RR intervals over the length of the recording (SDNN)/root mean square of successive differences in normal RR intervals (rMSSD) data to those without are detailed in online supplementary table S1.

**Figure 1** Study flow and inclusion and exclusion criteria.



### ECG and heart rate variability measures

A detailed description of ECG recordings in the SMART trial has been published elsewhere.<sup>16</sup> Briefly, identical electrocardiographs (GE MAC 1200 models, GE Milwaukee, Wisconsin, USA) were used in all of the study clinical sites, and standard 12-lead ECGs were recorded for all the participants using strictly standardised procedures. The digital ECG tracings stored in the electrocardiographs were transmitted regularly over analogue phone lines to the SMART ECG Reading Center, EPICARE, located at the Wake Forest School of Medicine, Winston-Salem, North Carolina for analysis. ECGs were evaluated blinded to the treatment group and ART use. After being visually checked for quality, the study ECGs were automatically processed using the 2001 version of the GE Marquette 12-SL program (GE, Milwaukee, Wisconsin). Heart rate variability indices were automatically calculated after excluding any ECG with non-sinus-originated beats (supraventricular and ventricular ectopic beats, atrioventricular blocks and atrial fibrillation) and artefacts. Two time-domain heart rate variability indices were calculated: the SDNN over the length of the recording and RMSSD.<sup>6</sup>

### Statistical analysis

Participants were categorised into one of the three groups based on the ART regimen they were receiving at the time of randomisation as follows: (1) boosted PI (PI/r), (2) non-boosted PI and (3) an NNRTI-no PI. The distribution of heart rate variability measures across these three groups was tabulated. Baseline characteristics were also summarised by these three ART groups. F tests were used to compare means,  $\chi^2$  tests to compare percentages.

Linear regression analysis was used to examine the association between heart rate and each of the heart rate variability measures, separately, with different ART regimens (PI/r and non-boosted PI regimens, separately, vs an NNRTI-no PI regimen). SDNN and rMSSD were log-transformed owing to their skewed distributions. Four different models were considered: model 1, unadjusted; model 2, adjusted for age, sex, race (Black, Asian, White and others) and NRTI backbone regimen; model 3, adjusted as in model 2 plus smoking status, total/high-density lipoprotein (HDL) cholesterol ratio, body mass index (BMI), prior cardiovascular disease, diabetes mellitus, use of blood pressure-lowering drugs and use of lipid-lowering drugs and model 4, adjusted as in model 3 plus baseline time since first prescribed ART, baseline CD4 T-cell count and plasma HIV RNA levels.

Two-sided p values are cited. A more stringent p value of <0.01 was considered significant to minimise type I error owing to multiple comparisons. Analyses were performed using SAS, V.9.1 (SAS Institute, Inc, Cary, North Carolina, USA) and R V.2.9.

### RESULTS

This analysis included 2998 participants. Average age was 44 years; 28% were women, 54% were white, 27% were

blacks and 6% were Asian. As shown in [table 1](#) and online supplementary table S2, 869 (29%) of the participants were receiving a PI/r (187 on saquinavir boosted with ritonavir, 410 on lopinavir boosted with ritonavir, 139 on atazanavir boosted with ritonavir (ATV/r) and 133 on other PI/r), 579 (19%) were receiving a non-boosted PI (345 on nelfinavir, 109 on indinavir, 84 on ATV and 41 on other PIs) and 1550 (52%) were receiving an NNRTI-no PI.

A number of baseline factors varied by the type of ART regimen used. Notably, most Asians (129 of 167) were receiving a PI/r while most blacks (426 out of 816) and whites (886 out of 1632) were receiving an NNRTI-no PI (unadjusted  $p < 0.001$ ). The highest levels of total cholesterol and the longer time since first prescribed ART, as well as the highest prevalence of the use of lipid-lowering drugs and lowest levels of baseline CD4 T-cell count, were observed in the PI/r group compared to the non-boosted PI and NNRTI-no PI groups (unadjusted  $p < 0.001$  for all comparisons). The highest prevalence of diabetes was observed in the non-boosted PI compared to the boosted PI and NNRTI-no PI groups. Participants on an NNRTI-no PI regimen were more likely to have HIV RNA <400 copies/ml and higher levels of HDL cholesterol compared to both PI-based regimens (unadjusted  $p < 0.001$ ; [table 1](#)).

[Figure 2](#) shows the distribution of heart rate variability measures in all study populations across different types of ART regimens. The median (IQR) values of the resting heart rate, SDNN and rMSSD in all study populations were 68 (61–77) beats/min (bpm), 20 (13–32) ms and 21 (13–34) ms, respectively. There was a positive correlation between SDNN and rMSSD (Spearman rank correlation ( $r$ )=0.88;  $p < 0.001$ ) but negative correlation between heart rate and SDNN ( $r$ =−0.39) and rMSSD ( $r$ =−0.55) with  $p$  value <0.001 for all.

There was no significant difference in heart rate, SDNN or rMSSD among individual boosted PIs and non-boosted PIs at an  $\alpha$ -level of 0.01 as shown in online supplementary table S2, and therefore, we combined all boosted PIs together and did the same for non-boosted PIs in the linear regression analysis.

[Table 2](#) shows the results of different regression models examining the association between PI-based regimens, compared to an NNRTI-no PI regimen, with heart rate, log SDNN and log rMSSD, separately. After adjustment for baseline factors (full model; model 4), among those given boosted PIs and non-boosted PIs, the heart rate was 2.2 and 2.8 bpm, respectively, lower than for the NNRTI-no PI group ( $p < 0.001$  for both). On the other hand, compared with the NNRTI-no PI group, log SDNN and log rMSSD were significantly greater for those in the non-boosted PI ( $p$  values for baseline adjusted differences in log-transformed SDNN and rMSSD were 0.004 and 0.001, respectively), but not those in the PI/r group at the 0.01  $\alpha$ -level ([table 2](#)).

In the full model (model 4), older age, higher total/HDL cholesterol ratio, higher BMI and diabetes were

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**Table 1** Baseline characteristics stratified by baseline antiretroviral use

Characteristic*	Boosted PI N=869	Non-boosted PI N=579	NNRTI-no PI N=1550	p Value**
Age (in years)	44.2±9.0	44.9±9.5	44.0±9.6	0.20
Gender (% female)	252 (29%)	178 (30.7%)	423 (27.3%)	0.27
Race				<0.001
Black	199 (22.9%)	191 (33%)	426 (27.5%)	
Asian	129 (14.8%)	7 (1.2%)	31 (2%)	
White	458 (52.7%)	288 (49.7%)	886 (57.2%)	
Other	83 (9.6%)	93 (16.1%)	207 (13.4%)	
Smoking status				0.47
Current smoker	316 (36.4%)	213 (36.8%)	613 (39.5%)	
Past smoker	223 (25.7%)	157 (27.1%)	390 (25.2%)	
Never smoker	330 (38%)	209 (36.1%)	547 (35.3%)	
Total cholesterol (mg/dl)	202.5±47.0	199.4±44.8	200.5±47.7	<0.001
LDL cholesterol (mg/dl)	115.0±34.6	120.0±35.9	116.8±35.6	0.44
HDL cholesterol (mg/dl)	42.8±14.0	41.2±14.4	46.2±14.9	<0.001
Triglycerides (mg/dl)	259.8±237.1	226.2±189.6	216.2±229.2	0.03
Total/HDL cholesterol	5.2±2.1	5.4±2.5	4.8±2.4	<0.001
Body mass index (kg/m <sup>2</sup> )	25.5±5.3	26.6±5.4	25.8±5.3	<0.001
Heart rate (bpm)	68.7±11.2	68.4±11.2	70.2±11.5	<0.001
Prior CVD	32 (3.7%)	24 (4.1%)	61 (3.9%)	0.90
Diabetes	46 (5.3%)	52 (9%)	121 (7.8%)	0.02
BP-lowering drugs	137 (15.8%)	118 (20.4%)	314 (20.3%)	0.02
Lipid-lowering drugs	173 (19.9%)	92 (15.9%)	262 (16.9%)	0.09
Baseline CD4 (cells/mm <sup>3</sup> )	640.4±239.0	711.6±265.6	690.8±262.2	<0.001
HIV RNA (% ≤400 copies/mL)	723 (83.4%)	434 (75%)	1357 (87.8%)	<0.001
Time since first prescribed ART (in years)	6.7±3.9	6.4±3.1	5.8±3.4	<0.001
Baseline NRTI regimen				<0.001
AZT+3TC (without ABC)	302 (34.8%)	280 (48.4%)	639 (41.2%)	
TNF (without ABC)	223 (25.7%)	30 (5.2%)	268 (17.3%)	
ABC (without TNF)	130 (15%)	65 (11.2%)	236 (15.2%)	
3TC+D4T	81 (9.3%)	132 (22.8%)	239 (15.4%)	
Other NRTI regimens	133 (15.3%)	72 (12.4%)	168 (10.8%)	

\*Values expressed as mean±SD or N (%).

\*\*Means were compared with F tests, X<sup>2</sup> tests for percentages; p value <0.01 is considered significant.

ABC, abacavir; AZT, zidovudine; BP, blood pressure; CVD, cardiovascular disease; D4T, stavudine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TNF, tenofovir; 3TC, lamivudine.

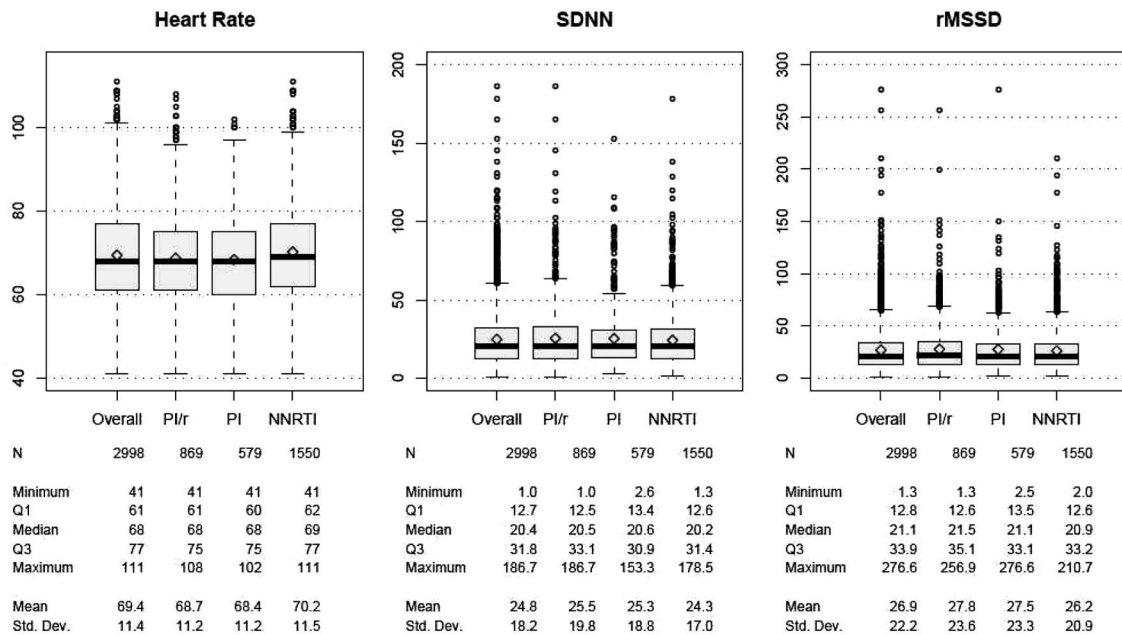
significantly associated with lower SDNN and rMSSD. There were no significant associations between baseline CD4 T-cell count, plasma HIV RNA levels and type of NRTI backbone regimen with any of the heart rate variability measures (see online supplementary table 3).

## DISCUSSION

The key findings of our study were as follows: (1) use of protease inhibitors, whether boosted or non-boosted, was associated with slower (favourable) resting heart rate compared to NNRTI-no PI use; (2) non-boosted PI use was associated with higher levels of heart rate variability measures (ie, better cardiac autonomic function) compared to NNRTI-no PI use; (3) no significant difference in heart rate variability measures between PI/r and NNRTI-no PI groups and (4) no significant differences in heart rate and heart rate variability measures among individual drugs in the PI/r and non-boosted PI groups, which suggest that the observed associations are class associations. The

clinical relevance of these observed differences in cardiac autonomic function among ART regimens and how they may influence cardiovascular outcomes in HIV-infected individuals need to be investigated.

Former studies that have been carried out in participants with and without cardiovascular disease showed that higher resting heart rate and lower heart rate variability are associated with poor prognosis in both the general population<sup>17–28</sup> and HIV-infected individuals.<sup>8–13</sup> These measures of cardiac autonomic function are dynamic rather than static, affected by disease processes as well as cardioactive medications. Given the reported higher prevalence of cardiac autonomic dysfunction in HIV-infected individuals and the reported atherogenic and diabetogenic effects of PIs, examining the association between this class of ART and autonomic function carries special importance. Since today's most relevant group of HIV-infected individuals receives ART, examining the association of protease inhibitors with cardiac autonomic function in comparison with other ART



**Figure 2** Distribution of resting heart rate variability measures across different types of antiretroviral treatment. PI, protease inhibitors; PI/r, boosted PI; NNRTI, non-nucleoside reverse transcriptase inhibitor; SDNN, the standard deviation of all filtered RR intervals over the length of the recording; RMSSD, the root mean square of the difference of successive RRs

regimens, rather than no treatment, provides more practical information. Hence, we examined the association between resting heart rate and heart rate variability (SDNN and rMSSD) with the use of PI-based regimens (boosted and non-boosted) compared to an NNRTI-no PI regimen.

In theory, an increase in resting heart rate could be due to lower parasympathetic and/or higher sympathetic tone.<sup>6–8</sup> On the other hand, the SDNN component of heart rate variability is a measure of the overall combined parasympathetic and sympathetic modulation of heart rate, while rMSSD reflects the degree of parasympathetic modulation. Thus, hypothetically, the slower resting heart rate accompanied by higher values of SDNN and rMSSD in the non-boosted PI group might reflect a favourable influence on both the sympathetic and parasympathetic modulation of the cardiac autonomic function. On the other hand, the lower values of resting heart rate accompanied by non-significant associations with SDNN and rMSSD in the boosted-PI group might reflect a favourable influence on the sympathetic but not the parasympathetic modulation of the cardiac autonomic function. Determining the exact mechanism by which non-boosted PIs can improve heart rate variability and autonomic cardiac regulation and why they differ from boosted PIs will require additional research. Nevertheless, a number of possible explanations could be hypothesised.

Autonomic dysfunction in untreated patients with advanced disease was generally believed to be caused by the HIV-1 virus itself, which is well known to be neurotropic.<sup>29–30</sup> So it is possible that suppression of the HIV virus by protease inhibitors might have reduced the

chances of developing cardiac autonomic dysfunction. Nevertheless, we did not find a significant difference in heart rate variability for those with plasma HIV RNA  $\leq 400$  vs  $>400$  copies/ml. Also, in a recent case-control study in which 97 HIV-infected individuals receiving ART for at least 12 months were compared to an age-matched control group of 52 healthy volunteers, autonomic dysfunction was present in the HIV-infected group even with a suppressed plasma HIV load by ART.<sup>4</sup> These results accord with another small study of 16 treated HIV individuals in whom reduced heart rate variability was found as well.<sup>8</sup> This suggests that viral suppression cannot fully explain the favourable association between non-boosted PIs (compared to NNRTI/no PI) in heart rate variability.

Differences between NNRTI and non-boosted PI regimens in heart rate variability could be the result of differences in the balance between their favourable viral suppression (even if it is not the major driving force) and their harmful atherogenic impacts. This could be partially supported by what we observed as differences in the lipid profile among different ART regimens. Similarly, several ART drugs have been associated with the development of toxic neuropathy.<sup>31–32</sup> Hence, another possibility is that differences in neurotoxicity might have resulted in differences in the associations of ART drugs with markers of cardiac autonomic function.

Our study has some limitations. Similar to any cross-sectional analysis, residual confounding by factors we did not consider or measure is a possibility. While we adjusted for many potentially confounding factors, information on antiarrhythmic drug use, which could affect resting heart rate and heart rate variability, was not collected in the

**Table 2** Differences in heart rate and heart rate variability between protease inhibitor-based regimens and NNRTI-based regimens

Measure	Model 1: unadjusted		Model 2: adjusted for age, gender, race and NRTI backbone		Model 3: adjusted for model 2 plus smoking status, total cholesterol/HDL ratio, BMI, history of CVD events* at baseline, diabetes, blood pressure-lowering drugs and lipid-lowering drugs		Model 4: adjusted for model 3 plus baseline time since first prescribed ART, baseline CD4 and HIV-RNA	
	Difference (95% CI)	p Value*	Difference (95% CI)	p Value*	Difference (95% CI)	p Value*	Difference (95% CI)	p Value*
Heart Rate (bpm)								
Boosted PI	-1.52 (-2.46 to -0.57)	0.002	-1.67 (-2.65 to -0.69)	<0.001	-1.93 (-2.91 to -0.96)	<0.001	-2.15 (-3.14 to -1.16)	<0.001
Non-boosted PI	-1.84 (-2.92 to -0.75)	<0.001	-2.08 (-3.18 to -0.98)	<0.001	-2.62 (-3.70 to -1.53)	<0.001	-2.81 (-3.90 to -1.71)	<0.001
NNRTI-no PI	Ref.	–	Ref.	–	Ref.	–	Ref.	–
SDNN (log 10 ms)								
Boosted PI	0.01 (-0.01 to 0.04)	0.35	0.01 (-0.01 to 0.04)	0.38	0.02 (-0.01 to 0.04)	0.19	0.02 (-0.01 to 0.05)	0.12
Non-boosted PI	0.02 (-0.01 to 0.05)	0.22	0.03 (0.00 to 0.06)	0.03	0.04 (0.01 to 0.07)	0.006	0.04 (0.01 to 0.07)	0.004
NNRTI-no PI	Ref.	–	Ref.	–	Ref.	–	Ref.	–
rMSSD (log 10 ms)								
Boosted PI	0.02 (-0.01 to 0.04)	0.22	0.01 (-0.01, 0.04)	0.27	0.02 (-0.00 to 0.05)	0.09	0.03 (0.00 to 0.05)	0.04
Non-boosted PI	0.02 (-0.01 to 0.05)	0.14	0.03 (0.00 to 0.06)	0.04	0.04 (0.01 to 0.07)	0.003	0.05 (0.02 to 0.08)	0.001
NNRT-no PI	Ref.	–	Ref.	–	Ref.	–	Ref.	–

\*p Value <0.01 is considered significant.

bpm, beats/min; ms, millisecond; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; rMSSD, the root mean square of successive differences in the RR intervals; SDNN, the SD of all filtered RR intervals over the length of the recording.

SMART trial. Nevertheless, by adjusting for blood pressure-lowering drugs which include  $\beta$ -blockers and calcium channel blockers, we have adjusted for class II ( $\beta$ -blockers) and class IV (calcium channel blockers) antiarrhythmic drugs—unless these agents were used specifically for arrhythmia and not for lowering blood pressure. Information on the exact time of HIV infection was not available and was practically difficult to obtain. However, we adjusted for the time since prescribed first ART, which is very likely correlated with the time of infection. Another limitation inherent to all cross-sectional analyses is the inability to confirm the temporal relationship between ART use and changes in the resting heart rate and heart rate variability. Despite these limitations, our study has many strengths. This is the first study to examine the association between various PI-based regimens and cardiac autonomic function in a large unselected cohort from a well-defined diverse population of HIV-infected individuals. A detailed medical history including ART use as well as clinical and laboratory data were available in the majority of our study population. Also, ECG acquisition was performed in a consistent manner by trained research staff, and the resting heart rate and heart rate variability were measured automatically (0% variability) in a central ECG core laboratory.

## CONCLUSION

Compared to an NNRTI-no PI regimen, both boosted and non-boosted PI regimens were associated with better (ie, slower) resting heart rate, but only non-boosted PI use was associated with better cardiac autonomic function manifested as higher levels of heart rate variability.

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**Acknowledgements** The authors would like to thank the SMART study investigators and participants. For a complete list of SMART investigators.<sup>14</sup>

**Contributions** EZS and JDN conceived the idea of the study. All authors provided input into the data interpretation. MPR conducted the statistical analysis. EZS drafted the manuscript. DAD, HK, RE and JDN critically revised the manuscript. JDN is the guarantor. All authors gave final approval for the submission of the manuscript.

**Funding** The SMART study was sponsored by the US National Institute of Allergy and Infectious Diseases, National Institutes of Health (grants U01AI042170, U01AI04636 and U01AI068641).

**Competing interests** None.

**Ethics approval** The Institutional Review Board approved the participating centres.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** No additional data are available.

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*BMJ Open* 2013 3:  
doi: 10.1136/bmjopen-2012-002523

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