Published in final edited form as:
AIDS. 2011 January 28; 25(3): 367–377. doi:10.1097/QAD.0b013e328341dcc0.

Boosted protease inhibitors and the electrocardiographic measures of QT and PR durations

Elsayed Z. Soliman[a], **Jens D. Lundgren**[b], **Mollie P. Roediger**[c], **Daniel A. Duprez**[d], **Zelalem Temesgen**[e], **Markus Bickel**[f], **Judith C. Shlay**[g], **Charurut Somboonwit**[h], **Peter Reiss**[i], **James H. Stein**[j], and **James D. Neaton**[c] **for the INSIGHT SMART Study Group**

[a] Epidemiological Cardiology Research Center (EPICARE), Department of Epidemiology and Prevention, Wake Forest University School of Medicine, Winston Salem, North Carolina, USA [b] Copenhagen HIV Program, State University Hospital and University of Copenhagen, Copenhagen, Denmark [c] Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis [d] Department of Medicine, University of Minnesota, Minneapolis [e] Division of Infectious Diseases, Mayo Clinic and Foundation, Rochester, Minnesota, USA [f] HIV Medical Treatment and Research Unit, JW Goethe University, Frankfurt, Germany [g] Denver Community Programs for Clinical Research on AIDS, Denver, Colorado [h] Division of Infectious Disease and International Medicine, University of South Florida College of Medicine, Tampa, Florida, USA [i] Department of Medicine, Amsterdam Institute for Global Health and Development and Center for Infection and Immunity, Academic Medical Center, Amsterdam, The Netherlands [j] University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

Abstract

Background—There are contradictory reports regarding the effects of protease inhibitors on the ECG measures of QT and PR interval durations. The effect of interrupting use of protease inhibitors on QT and PR progression is also unknown.

Methods—This analysis included 3719 participants from the Strategies for Management of Antiretroviral Therapy (SMART) study, of whom 1879 were randomized to receive intermittent antiretroviral therapy (ART) (drug conservation group), whereas the rest received these drugs continuously (viral suppression group). Linear regression analysis was used to compare four ritonavir-boosted protease inhibitor (protease inhibitor/r) regimens [saquinavir (SQV/r), lopinavir (LPV/r), atazanavir (ATV/r), and other protease inhibitor/r], and nonboosted protease inhibitor regimens with nonnucleoside reverse transcriptase inhibitor (NNRTI) regimens for Bazett's (QTcB) and Fredericia's (QTcF) heart rate corrected QT and PR. Changes in QTcB, QTcF, and PR after 12 and 24 months of randomization were compared in the drug conservation group and viral suppression group.

Results—Average levels of QTcB, QTcF, and PR duration at entry were 415, 406, and 158 ms. At study entry, 49% of participants were taking an NNRTI (no protease inhibitor)-based regimen and 31% were prescribed a boosted protease inhibitor, the most common being LPV/r. After adjustment for baseline factors, QTcB and QTcF levels did not vary by boosted protease inhibitor group ($P = 0.26$ and $P = 0.34$, respectively). For those given any of the boosted protease inhibitors, QTcB was 1.5 ms lower than the NNRTI group ($P = 0.04$). Both boosted and nonboosted protease inhibitor-containing regimens were significantly associated ($P < 0.01$ for

Correspondence to Elsayed Z. Soliman, MD, MSc, MS, Epidemiological Cardiology Research Center (EPICARE), Department of Epidemiology and Prevention, Wake Forest University School of Medicine, 2000 West First St., Piedmont Plaza 2, Suite 505, Winston Salem, NC 27104, USA. Tel: +1 336 716 8632; fax: +1 336 716 0834; esoliman@wfubmc.edu.

each) with longer PR intervals compared to the NNRTI group. After adjustment, the difference between boosted protease inhibitors and the NNRTI group was 5.11 ms (P <0.01); for nonboosted protease inhibitors, this difference was 3.00 ms (P <0.01). Following ART interruption, PR duration declined for both the boosted and nonboosted protease inhibitor groups and compared to the viral suppression group, significant changes in PR interval were observed 24 months after ART interruption of boosted protease inhibitors (P <0.01).

Conclusion—Different protease inhibitor-based regimens have a similar, minimal effect on QT compared to NNRTI-based regimens. All protease inhibitor-based regimens (boosted and nonboosted) were associated with prolongation of PR, and interruption of protease inhibitor regimens reduced the prolonged PR duration. Further research is needed to confirm the findings of this study and assess the clinical relevance of the differences.

Keywords

electrocardiogram; HIV/AIDS; PR; protease inhibitors; QTc

Introduction

Despite the known benefits of protease inhibitors, there have been concerns about their potential adverse effects on cardiac conductivity manifested as prolongation of QT and PR interval durations in the standard electrocardiogram (ECG) [1]. A number of case reports and small single center studies have reported prolongation of QTc and PR in patients receiving protease inhibitors [2–5], but others reported the opposite [6,7].

In the past 2 years, the Food and Drug Administration (FDA) has issued warnings that ritonavir-boosted lopinavir (LPV/r) and ritonavir-boosted saquinavir (SQV/r) may cause prolongation of QTc and PR [8,9]. Nevertheless, with the current conflicting reports, it is hard to derive a definitive conclusion about the association between protease inhibitors, especially those boosted with ritonavir, which may enhance the bioavailability of the boosted protease inhibitor [10]. Also, it is not clear whether discontinuation of protease inhibitor-based regimens results in normalization of QTc and PR and how long it takes for these ECG markers to return to normal.

The purpose of this analysis was to compare QTc and PR durations at study entry in participants using nonboosted and ritonavir-boosted protease inhibitor regimens with those in participants using nonnucleoside reverse transcriptase inhibitors (NNRTIs) and to compare the effect of continuous versus interrupted use of ritonavir-boosted protease inhibitor and other antiretroviral therapy (ART) regimens on QTc and PR after 12 and 24 months. The Strategies for Management of Antiretroviral Therapy (SMART) study, a clinical trial that compared continuous versus interrupted use of ART, provides a unique opportunity to address both of these issues.

Methods

The Strategies for Management of Antiretroviral Therapy (SMART) study

The SMART study was an open-label randomized trial comparing two ART strategies [11,12]. The viral suppression strategy (viral suppression group) was designed to be consistent with the guidelines for the use of ART agents in HIV-infected adults and adolescents [13]; that is, all available ART regimens were to be used in an uninterrupted manner with the goal of maximal and continuous suppression of HIV replication. The experimental drug conservation strategy (drug conservation group) entailed the episodic use of ART according to prespecified $CD4^+$ cell count thresholds; that is, ART was to be

interrupted until the $CD4^+$ cell count decreased to less than 250 cells per cubic millimeter, at which time ART was to be reinitiated and continued until the $CD4^+$ cell count increased to more than 350 cells per cubic millimeter. On 10 January 2006, the data and safety monitoring board recommended stopping enrollment in the SMART study because of a safety risk in the drug conservation group. After a change in protocol, participants who had previously received ART in the drug conservation group were advised to reinitiate ART. All participants were followed for another 1.5 years [12].

Study population

All SMART participants (*N*= 5472) were considered eligible for the present analysis, except those who were off ART, on an ART regimen not containing a protease inhibitor and/or an NNRTI at baseline or on an ART regimen not containing a nucleoside reverse transcriptase inhibitor (NRTI), who were missing their baseline ECG or those with ECG conditions that interfere with appropriate measurement of PR and/or QT. After these exclusions, 3719 participants remained and were included in this analysis (Fig. 1).

Data collection and follow-up—Before randomization, an ART and medical history were obtained and $CD4^+$ cell count and HIV-RNA level were measured. Follow-up visits were scheduled monthly for the first 2 months, every 2 months thereafter for the first year, and every 4 months in the second and subsequent years. At each visit, a medical and ART history was taken and $CD4^+$ cell count and HIV-RNA level were measured. At the baseline visit and at each annual visit, a 12-lead ECG was obtained.

Ascertainment of ECG abnormalities

Identical electrocardiographs (GE MAC 1200 models; GE, Milwaukee, Wisconsin, USA) were used in all SMART clinics and standard 12-lead ECGs were recorded in all participants by strictly standardized procedures. The digitally recorded ECGs were transmitted regularly over phone lines to the SMART central ECG Reading Center, EPICARE, located at Wake Forest University, Winston Salem, North Carolina for analysis. ECGs were evaluated blinded to treatment group and ART used. The study ECGs were automatically processed (after being visually checked for quality) using the 2001 version of the GE Marquette 12-SL program (GE). Heart rate corrected QT (QTc) was calculated using Bazett's ($QTcB = QT^* [\text{heart rate}/60]^{1/2}$) [14] and Fredericia's ($QTcF = QT^* [\text{heart rate}/60]^{1/3}$) [15] formulae. Because the PR interval is also heart rate-dependent [16], we adjusted for baseline heart rate in all of the PR models. In this analysis, ECG data from the baseline, month-12 and month-24 visits were used.

Statistical analysis

Based on the ART regimen which participants were receiving at the time of randomization, patients were categorized into one of six groups: SQV/r; LPV/r; atazanavir boosted with ritonavir (ATV/r); other ritonavir boosted protease inhibitors (protease inhibitor/ritonavir); any nonboosted protease inhibitor; or an NNRTI without a protease inhibitor.

Linear regression analysis was used to compare baseline values of QTcB, QTcF and PR for SQV/r, LPV/r, ATV/r, other protease inhibitor/ritonavir, and nonboosted protease inhibitor compared to an NNRTI, no protease inhibitor regimen (reference value). Four different models were considered: model 1 [unadjusted], model 2 [adjusted for age, sex, race (black, Asian, white (referent), and others) and NRTI backbone regimen], model 3 [adjusted as in model 2 and smoking status, total/high-density lipoprotein (HDL) cholesterol ratio, body mass index (BMI), prior cardiovascular disease (CVD), diabetes mellitus, use of blood pressure-lowering drugs and use of lipid-lowering drugs], and model 4 (adjusted as in model 3 and duration of HIV infection, baseline CD4 cell count and HIV-RNA levels). All PR

models were additionally adjusted for the heart rate. With this same approach, we also assessed whether QTcB, QTcF, and PR varied among the four boosted protease inhibitor groups.

Changes in QTcB, QTcF, and PR after 12 and 24 months were examined separately within each treatment group according to protease inhibitor used at entry. We also compared changes in these ECG measures between the drug conservation (interrupted use) and viral suppression (continuous use) groups. Those taking ATV/r were combined with other protease inhibitor/ritonavir groups in this part of the analysis. Two analyses were carried out: an 'on-treatment' analysis, which excluded viral suppression patients who changed their ART regimen following baseline and drug conservation patients who reinitiated ART prior to the 12-month and 24-month follow-up visit; and an 'intention-to-treat' analysis, in which all participants meeting the criteria in Figure 1 and with a follow-up ECG at the designated visit (12 or 24 months) were included. The results of 'intention-to-treat analysis' are shown in the supplementary materials. Comparisons of changes in QTcB, QTcF, and PR between the drug conservation and viral suppression groups are adjusted for demographic, clinical and HIV characteristics at entry. Two-sided *P* values and 95% confidence intervals (CIs) are cited. SAS, version 9.1 (SAS Institute Inc., Cary, North Carolina, USA) was used in all analyses.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. E.Z.S., M.P.R., and J.D.N. had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

Results

Characteristics of the study population

The analysis included 3719 participants (Fig. 1), of whom 27% were women, 55% were white, 28% were black, and 5.3% were Asian. Mean age was 44 years. Approximately, 31% of the participants were receiving protease inhibitor/ritonavir regimens. SQV/r, LPV/r, and ATV/r were the most commonly used protease inhibitor/ritonavir regimens. In the 'other protease inhibitor/ritonavir' group, indinavir/ritonavir (95 participants) was the most common. Characteristics of the study population at baseline according to HIV treatment regimen are shown in Table 1. A number of factors varied by type of ART regimen used. Notably, the percentage of women (44%) and Asians (60%) prescribed SQV/r were much higher than the other groups. The majority of participants prescribed SQV/r (60%) were enrolled by sites in Thailand.

Associations with QTc interval

QTcB duration was longer than QTcF duration in all subgroups (Table 2). In these univariate analyses, those in the SQV/r subgroup showed greater values of QTcB and QTcF as well as a greater percentage with abnormal QTcB and QTcF (using 440 ms as a cut-point). However, no participants in any of the protease inhibitor/ritonavir subgroups had extreme QTcB or QTcF values (≥500 ms; Table 2).

Table 3 gives the baseline unadjusted and adjusted differences between each of the five protease inhibitor regimens and the NNRTI, no protease inhibitor regimen. Also shown are unadjusted and adjusted differences between all boosted protease inhibitor groups combined and the NNRTI group. Differences between regimens varied by the method of QT heart rate correction, whether QTcB or QTcF. In the unadjusted models and compared to NNRTI-

containing regimens (no protease inhibitor), SQV/r use was associated with prolongation of both QTcB and QTcF ($P<0.01$), LPV/r was associated with shortening of QTcB ($P<0.01$), and nonboosted protease inhibitor use was associated with prolongation of QTcF ($P= 0.02$). The difference between ATV/r or other protease inhibitor/ritonavir groups and the NNRTI group was not statistically significant for QTcB or QTcF. Except for SQV/r, these associations persisted after multivariable adjustment for demographic and clinical/HIV characteristics (models 2–4, Table 3). The adjustment for race had a large impact on the QTcB and QTcF differences between SQV/r and the NNRTI group. As shown in Supplemental Table 1, http://links.lww.com/QAD/A101 QTcB is higher for Asians than whites by 6.62 ms and, as previously noted, a higher percentage of Asians were prescribed SQV/r (Table 1). To explore this further, we carried out analyses by race. Adjusted differences between the SQV/r group and NNRTI-containing regimen (no protease inhibitor) group were 2.25 ms (95% CI: −7.66–12.16; $P= 0.65$) for Asians, 0.35 (95% CI: −9.19–9.88; $P= 0.94$) for blacks, 0.38 (95% CI: −4.24–5.01; $P= 0.87$) for whites, and −3.65 ms (95% CI: −12.38–5.08; $P= 0.41$) for participants in other race groups. These differences did not differ by race ($P= 0.47$).

We also considered whether there was significant variation in QTcB and QTcF among the four boosted protease inhibitor groups. Neither adjusted levels of QTcB nor adjusted levels of QTcF varied significantly ($P= 0.26$ and $P= 0.34$ for QTcB and QTcF, respectively). For all boosted protease inhibitors combined versus the NNRTI group, the average difference in QTcB at baseline after adjustment for baseline covariates (model 4) was −1.53 ms (95% CI: −2.95 to −0.10; $P= 0.04$). For QTcF, this difference was 0.60 ms (95% CI: −0.82 to 2.01; $P= 0.41$).

In the full model (model 4) for QTcB, older age, female sex, Asian race, BMI, and use of blood pressure-lowering drugs were associated with greater levels; for QTcF, older age, female sex, diabetes, and use of blood pressure-lowering drugs were associated with greater levels. Higher total/HDL cholesterol ratios and prior CVD were associated with lower levels of QTcF. For both QTcB and QTcF, levels varied among NRTIs used ($P= 0.004$ for QTcB and $P= 0.001$ for QTcF). Those taking a tenofovir-containing regimen or stavudine and lamivudine (d4T +3TC) had lower levels of QT than those taking zidovudine and 3TC (ZDV+3TC). (Supplemental Table 1, http://links.lww.com/QAD/A101).

Changes in QTc after 12 and 24 months of interrupted versus continuous antiretroviral therapy use

Table 4 and Table 5 summarize the changes in baseline QTcB and QTcF interval durations after 12 and 24 months of follow-up for participants with both baseline and month-12 or month-24 ECGs. These analyses are not protected by randomization as participants who reinitiated ART in the drug conservation group and those who changed their treatment regimen in the viral suppression group are excluded. In the viral suppression group, for which sample sizes are larger, durations of QTcB and QTcF in all groups did not significantly change after 12 or 24 months of continuous ART use. In the drug conservation group, QTcB levels did not change significantly from baseline; QTcF declined for each boosted protease inhibitor group with greater declines after 24 months. The changes in QTcB among those who discontinued different boosted protease inhibitors did not differ significantly from one another at 12 months ($P= 0.89$) or 24 months ($P= 0.73$). Likewise, the changes in QTcF did not differ significantly at 12 months ($P= 0.96$) or 24 months ($P= 0.30$). For the combined boosted protease inhibitor groups, QTcF declined significantly at 12 months (−3.27 ms; $P= 0.03$) and 24 months (−7.79 ms; $P= 0.01$) among participants in the drug conservation group who discontinued a boosted protease inhibitor. QTcF changes differed between the drug conservation and viral suppression groups for both those taking

any protease inhibitor/ritonavir and those in the nonboosted protease inhibitor group after 12 months (P= 0.04 for both) and 24 months (P<0.01 and 0.03, respectively).

We also carried out an 'intention-to-treat' analysis (see Supplemental Tables 2 and 3, http://links.lww.com/QAD/A101). For any protease inhibitor/ritonavir group, changes in QTcF for the drug conservation group and drug conservation-viral suppression differences in QTcF were reduced in these analyses as compared to those in Tables 4 and 5.

Associations with PR duration

The mean PR interval duration in all participants was 158.1 ms (±23.1). In univariate analyses, among participants in the LPV/r group, a greater percentage had durations greater than or equal 200 ms compared to those in the NNRTI group (6.6 versus 2.8%; P= 0.02). Percents for the other protease inhibitor/ritonavir groups ranged from 3.0 to 6.0%. Extreme values (≥300 ms) were observed in only two participants, both in the other protease inhibitor/ritonavir group (Table 2).

As shown in Table 3, in the unadjusted models, those taking protease inhibitor-containing regimens (boosted and nonboosted) had longer PR duration than those in the NNRTI group. Differences between each protease inhibitor group and the NNRTI group in PR duration were reduced with adjustment. Adjusted levels of PR durations did not vary significantly among the four boosted protease inhibitor groups (P= 0.56). For all boosted protease inhibitors combined versus the NNRTI group, the average difference in PR duration baseline after adjustment (model 4) was 5.11 ms (95% CI: 3.35–6.86; P<0.01).

In the full model (model 4), lower heart rate, older age, male sex, black and Asian race, higher total/HDL cholesterol ratio, higher BMI, and use of blood pressure-lowering drugs were associated with longer PR intervals. Current and past smokers had lower PR durations than those who never smoked (Supplemental Table 1, http://links.lww.com/QAD/A101).

Change in PR after 12 and 24 months of interrupted versus continuous antiretroviral therapy use

Table 4 and Table 5 summarize the change in baseline PR interval duration after 12 and 24 months of continuous versus interrupted use of ART in participants who had both baseline and month-12 or month-24 ECGs and had not either re-initiated ART (drug conservation group) or changed their treatment regimen (viral suppression group) through the indicated follow-up period (on-treatment analysis). No statistically significant changes were observed in the viral suppression group after 12 or 24 months. However, PR duration significantly shortened at 12 months among drug conservation participants who discontinued taking any boosted protease inhibitor at 12 and 24 months. Significant reductions in PR duration were also observed at 12 months among those who discontinued nonboosted protease inhibitors. The changes in PR duration among those who discontinued different boosted protease inhibitors did not differ significantly from one another at 12 months (P= 0.84) or 24 months (P= 0.36). A significant difference (P<0.01) in change in PR duration at 24 months between the drug conservation and viral suppression groups was evident for those taking a boosted protease inhibitor. The 'intention-to-treat' analyses (Supplemental Tables 2 and 3, http://links.lww.com/QAD/A101) showed that there was no significant change in PR interval after either 12 or 24 months of discontinuation of protease inhibitor-based regimens.

Unwitnessed sudden deaths

Fifteen participants died suddenly without a witness. Out of these, three participants had reported a prior history of CVD at baseline, but none had a CVD event during follow-up. These three participants reported having a myocardial infarction prior to randomization; two

of them additionally reported having coronary artery disease requiring surgery prior to randomization.

The average level of QTcB, QTcF, and PR duration for these 15 participants were 423, 408, and 141 ms, respectively. None of these unwitnessed deaths occurred in the SQV/r group. The deaths occurred in the LPV/r group (three deaths, 0.5%), other protease inhibitor/ritonavir group (one death, 0.5%), nonboosted protease inhibitor group (three deaths, 0.4%), and NNRTI-no protease inhibitor group (eight deaths, 0.4%).

Discussion

We examined differences in QTc and PR duration among different protease inhibitor-based regimens and an NNRTI-based regimen, and the impact of ART interruption on these ECG measures. We studied QTc and PR as continuous variables in the multivariable adjusted analysis to increase power and to avoid choosing cut-points that appear to vary in terms of the normal values and prognostic significance between men and women and between race groups [17–23].

The key findings from comparisons at baseline were as follows: unadjusted levels of QTcB and QTcF were greater for those on SQV/r than those in the NNRTI (no-protease inhibitor) group; however, these differences did not persist after adjustment (primarily for Asian race); in adjusted analyses, average QTcB and QTcF levels did not vary by boosted protease inhibitor group, and average QTcB was significantly lower for any protease inhibitor/ritonavir group compared to the NNRTI group; and protease inhibitor-containing regimens (boosted and nonboosted) were significantly associated with longer PR intervals compared to the NNRTI group. Key findings from the analyses of change after 12 and 24 months were as follows: QTc interval and PR duration did not change significantly for those in the viral suppression group (continuous ART) for any of the ART subgroups; QTcF, but not QTcB, declined following discontinuation of boosted protease inhibitor regimens, and compared to the viral suppression group, the changes at 12 and 24 months were significantly different (relative to the viral suppression group, levels of QTcF also declined for participants in the nonboosted protease inhibitor group); and PR duration declined for both boosted and nonboosted protease inhibitors in the drug conservation group and compared to the viral suppression group, significant changes in PR interval were observed 24 months after ART interruption of boosted protease inhibitors.

In February 2010, the FDA announced that there is an ongoing review of clinical trial data to investigate the effects of SQV/r on QTc and PR intervals [9]. Also, in April 2009, the FDA changed the label of LPV/r (Kaletra) to include caution regarding potential prolongation of QTcF and PR in some patients [8]. In our investigation, after adjustment for baseline covariates, there was no evidence that any of the boosted protease inhibitors prolonged QT. In fact, as a group, average levels of QTcB were lower for those taking boosted protease inhibitors compared to those taking an NNRTI-based regimen. This was most evident for the large group of participants taking LPV/r. In these analyses, we noted a substantial confounding effect of Asian race. This had a greater effect on SQV/r as many more Asian participants were taking that treatment. The higher QT levels for Asians compared to other race groups are consistent with other studies [22,23]. Without the adjustment for Asian race, both QTcB and QTcF were significantly greater for the SQV/r group than the NNRTI group. With respect to PR duration, consistent with the concerns raised by the FDA, we found that for all of the protease inhibitor regimens considered, PR duration was increased compared to those taking an NNRTI.

Short QTc has been linked to arrhythmogenesis and sudden death, and both long and short QT share common pathophysiological and molecular basis [24,25]. Therefore, the FDA concerns about the effect of boosted protease inhibitors on the heart may remain valid, but perhaps for a different reason. Alternatively, NNRTI-containing regimens may be associated with greater prolongation of QTc compared to LPV/r. Considering our data on changes in QTcB through 12 and 24 months, it seems likely that the effect of boosted protease inhibitors on QTcB levels is minimal (at baseline, the average difference was −1.53 ms between the all boosted protease inhibitors and the NNRTI group). Some previous reports have shown no prolonging effect of LPV/r [6,7], which accords with the latter explanation.

The PR interval is a measure of atrioventricular node function as well as atrial conduction [26]. Prolongation of PR interval could be an early manifestation of an ongoing conduction defect that may lead eventually to complete atrioventricular block. In the general population, prolonged PR has been shown to predict atrial fibrillation [27,28] and mortality [29]. The prevalence of abnormal PR (>200 ms) was more in the LPV/r users; however, differences in average levels among the boosted protease inhibitor groups did not vary significantly, and levels were also higher in the nonboosted protease inhibitor group compared to the NNRTI group. With interruption, PR durations declined, suggesting a direct effect of protease inhibitors. For those continuing on their protease inhibitor regimens in the viral suppression group, there was no further increase in PR duration. For HIV participants, prolongation of PR should be interpreted with caution. Studies are needed to examine the molecular and genetic basis of drug-induced prolongation of PR as well as the prognostic significance and clinical relevance of such prolongation in HIV-infected population. In the general population, a 20 ms higher PR duration was associated with an 8% increase in all-cause mortality [29]. At entry, the average difference in PR duration between those taking a boosted protease inhibitor regimen and an NNRTI regimen was only 5 ms. The clinical relevance of this difference is uncertain.

Our study has some limitations. Comparisons of QTc and PR intervals among different ART at entry are subject to possible confounding by factors we either did not consider or measure. The potential effect of unmeasured confounders is illustrated with the striking effect of adjustment for Asian race on SQV/r levels. Although we adjusted for many potentially confounding factors, information on QTc-prolonging drugs that are commonly used in HIV/AIDS patients (e.g., methadone) was not available to us, which is a major limitation. Also information on antiarrhythmic drug use, which may affect QTc and PR was not collected in SMART. Nevertheless, by adjusting for blood pressure-lowering drugs, which include β-blockers and calcium channel blockers, we have adjusted for class II (β-blockers) and class III (calcium channel blockers) antiarrhythmic drugs – unless these agents were used specifically for arrhythmia not for blood pressure. Information on the baseline duration of receiving ART was not collected. However, we adjusted for the baseline duration of HIV infection, which is likely correlated with the duration of taking ART. Another limitation is that ECGs were only recorded annually. By 1 year, many of the participants in the drug conservation group had reinitiated ART. This resulted in small sample sizes for some of the protease inhibitor/ritonavir subgroups. In addition, the ‘on-treatment’ analyses, though adjusted for several factors, are also subject to unmeasured confounders.

Despite the above-mentioned limitations, our study has many strengths that warrant highlighting. This is the first to examine the effects of various protease inhibitor-based regimens on key measures of cardiac conductivity in a large unselected cohort from a well defined diverse population of HIV-infected patients. This contrasts with prior reports, which were based largely on case reports and case series. Detailed medical history, including ART use as well as clinical and laboratory data were available in the majority of our study

population. ECGs were conducted in a consistent manner by trained research staff, QT and PR intervals were measured automatically (0% variability) in a central ECG core laboratory and we used two different QT heart rate correction formulae to confirm the results. In addition, this study is the first to evaluate the effect of discontinuation of protease inhibitor-containing regimens on these intervals in a prospective manner from a large cohort.

Conclusion

Different protease inhibitor-based regimens have a similar, minimal effect on QT compared to NNRTI-based regimens. All protease inhibitor-based regimens (boosted and nonboosted) were associated with prolongation of PR, and interruption of protease inhibitor regimens reduced PR duration. These results should not limit the use of protease inhibitor/ritonavir regimens when indicated, as the clinical relevance of these findings requires further research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The SMART study was sponsored by the National Institute of Allergy and Infectious Disease, National Institutes of Health (grants U01AI042170, U01AI46362, and U01AI068641).

J.H.S. serves on data and safety monitoring boards for non-HIV-related research studies sponsored by Abbott, Lilly, and Takeda. P.R. reported serving as a scientific advisor to Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmith-Kline, Merck, Theratechnologies, Tibotec Therapeutics, and Tobira Therapeutics; has served on data and safety monitoring boards and endpoint adjudication committees for Tibotec Therapeutics; has received honoraria for speaking engagements at scientific conferences from Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, and Theratechnologies; and has received research support from Gilead Sciences, ViiV Health-care, and Boehringer Ingelheim Pharmaceuticals. B.M. has received travel support, lecture or consultant fees from Abbott, Boehringer Ingelheim, Gilead Sciences, GlaxoSmithKline, Merck Sharp Dome, Roche Diagnostics and Tibotech. Z.T. is on advisory board –of Gilead, Merck, and ViiV and received research and education grants from Pfizer, Gilead and Tibotec.

References

1. Singh M, Arora R, Jawad E. HIV protease inhibitors induced prolongation of the QT interval: electrophysiology and clinical implications. Am J Ther. 2009 [Epub ahead of print].
2. Anson BD, Weaver JG, Ackerman MJ, Akinsete O, Henry K, January CT, et al. Blockade of HERG channels by HIV protease inhibitors. Lancet. 2005; 365:682–686. [PubMed: 15721475]
3. Ly T, Ruiz ME. Prolonged QT interval and torsades de pointes associated with atazanavir therapy. Clin Infect Dis. 2007; 44:e67–e68. [PubMed: 17304444]
4. Chinello P, Lisena FP, Angeletti C, Boumis E, Papetti F, Petrosillo N. Role of antiretroviral treatment in prolonging QTc interval in HIV-positive patients. J Infect. 2007; 54:597–602. [PubMed: 17174400]
5. Rathbun CR, Liedtke MD, Blevins SM, Harrison D, Lockhart SM, et al. Electrocardiogram abnormalities with atazanavir andLPV/ronavir. HIV Clin Trials. 2009; 10:328–336. [PubMed: 19906626]
6. Charbit B, Rosier A, Bollens D, Boccara F, Boelle PY, Koubaa A, et al. Relationship between HIV protease inhibitors and QTc interval duration in HIV-infected patients: a cross-sectional study. Br J Clin Pharmacol. 2009; 67:76–82. [PubMed: 19076152]
7. Busti AJ, Tsikouris JP, Peeters MJ, Das SR, Canham RM, Abdullah SM, et al. A prospective evaluation of the effect of atazanavir on the QTc interval and QTc dispersion in HIV-positive patients. HIV Med. 2006; 7:317–322. [PubMed: 16945077]

8. U.S. Food and Drug Administration. Labeling changes for Kaletra reflecting new QT/QTC interval and PR interval prolongation information. April. 2009 http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/hivandaidsactivities/ucm155697.htm
9. U.S. Food and Drug Administration. Invirase (saquinavir): ongoing safety review of clinical trial data. February. 2010 http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm201563.htm
10. Zeldin RK, Petruschke RA. Pharmacological and therapeutic properties of ritonavir-boosted protease inhibitor therapy in HIV-infected patients. J Antimicrob Chemother. 2004; 53:4–9. [PubMed: 14657084]
11. The SMART Study Group. CD4+ count-guided interruption of antiretroviral therapy. N Engl J Med. 2006; 355:2283–2296. [PubMed: 17135583]
12. SMART Study Group. Risk for opportunistic disease and death after reinitiating continuous antiretroviral therapy in patients with HIV previously receiving ePIodic therapy, a randomized trial. Ann Int Med. 2008; 149:289–299. [PubMed: 18765698]
13. Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. December. 2009 http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf
14. Bazett HC. An analysis of the time-relations of electrocardiogram. Heart. 1920; 7:353–370.
15. Fridericia S. The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease. Acta Med Scand. 1920; 53:469–486.
16. Carruthers SG, McCall B, Cordell BA, Wu R. Relationships between heart rate and PR interval during physiological and pharmacological interventions. Br J Clin Pharmacol. 1987; 23:259–265. [PubMed: 2882775]
17. U.S. Food and Drug Administration. Guidance for industry. E14 clinical evaluation of QT/QTc interval prolongation and pro-arrhythmic potential for nonantiarrhythmic drugs. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129357.pdf
18. Indik JH, Pearson EC, Fried K, Woosley RL. Bazett and Fridericia QT correction formulas interfere with measurement of drug-induced changes in QT interval. Heart Rhythm. 2006; 3:1003–1007. [PubMed: 16945790]
19. Luo S, Michler K, Johnston P, Macfarlane PW. A comparison of commonly used QT correction formulae: the effect of heart rate on the QTc of normal ECGs. J Electrocardiol. 2004; 37:81–90. [PubMed: 15534815]
20. Rautaharju PM, Warren JW, Calhoun HP. Estimation of QT prolongation. A persistent, avoidable error in computer electrocardiography. J Electrocardiol. 1990; 23:111–117. [PubMed: 2090728]
21. Rautaharju, PM.; Rautaharju, F. Investigative Electrocardiography in Epidemiological Studies and Clinical Trials. Berlin: Springer; 2007. QT prolongation and QT dispersion: a critical evaluation.
22. Grandinetti A, Seifried S, Mor J, Chang HK, Theriault AG. Prevalence and risk factors for prolonged QTc in a multiethnic cohort in rural Hawaii. Clin Biochem. 2005; 38:116–122. [PubMed: 15642272]
23. Rautaharju PM, Prineas RJ, Kadish A, Larson JC, Hsia J, Lund B. Normal standards for QT and QT subintervals derived from a large ethnically diverse population of women aged 50 to 79 years (the Women's Health Initiative [WHI]). Am J Cardiol. 2006; 97:730–737. [PubMed: 16490447]
24. Brugada R, Hong K, Dumaine R, Cordeiro J, Gaita F, Borggrefe M, et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. Circulation. 2004; 109:30–35. [PubMed: 14676148]
25. Itoh H, Horie M, Ito M, Imoto K. Arrhythmogenesis in the short-QT syndrome associated with combined HERG channel gating defects: a simulation study. Circ J. 2006; 70:502–508. [PubMed: 16565572]
26. Chou, T.; Knilans, TK. Electrocardiography in clinical practice. 4. Philadelphia, PA: W.B. Saunders; 1996.
27. Soliman EZ, Prineas RJ, Case D, Zhang ZM, Goff DC Jr. Ethnic distribution of electrocardiographic predictors of atrial fibrillation and its impact on understanding the ethnic

distribution of ischemic stroke in the Atherosclerosis Risk in Communities Study (ARIC). Stroke. 2009; 40:1204–1211. [PubMed: 19213946]

28. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB Sr, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet. 2009; 373:739–745. [PubMed: 19249635]
29. Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D, et al. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. JAMA. 2009; 301:2571–2577. [PubMed: 19549974]

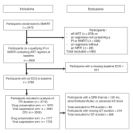

Fig. 1. Study flow diagram

ART, antiretroviral therapy; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

AIDS. Author manuscript; available in PMC 2012 January 28.

Table 1

Baseline characteristics stratified by the baseline antiretroviral use.

		Boosted protease inhibitors (*N* = 1156)					
	All population	**SQV/r**	**LPV/r**	**ATV/r**	**Other PI/r**	**Nonboosted PI**	**NNRTI – no PI**
	***N* = 3719**	***N* = 236**	***N* = 548**	***N* = 188**	***N* = 184**	***N* = 742**	***N* = 1821**
Age (in years)	44.4 ± 9.4	41.1 ± 8.6	44.8 ± 8.9	45.6 ± 9.5	45.4 ± 8.2	45.2 ± 9.3	44.1 ± 9.6
Sex (% female)	1007 (27.1%)	103 (43.6%)	136 (24.8%)	42 (22.3%)	28 (15.2%)	212 (28.6%)	486 (26.7%)
Race (%)							
Black	1026 (27.6%)	19 (8.1%)	157 (28.6%)	48 (25.5%)	54 (29.3%)	243 (32.7%)	505 (27.7%)
Asian	196 (5.3%)	142 (60.2%)	6 (1.1%)	1 (0.5%)	1 (0.5%)	10 (1.3%)	36 (2.0%)
White	2055 (55.3%)	60 (25.4%)	325 (59.3%)	123 (65.4%)	106 (57.6%)	383 (51.6%)	1058 (58.1%)
Other races	442 (11.9%)	15 (6.4%)	60 (10.9%)	16 (8.5%)	23 (12.5%)	106 (14.3%)	222 (12.2%)
Current smoker	1421 (38.2%)	58 (24.6%)	216 (39.4%)	82 (43.6%)	65 (35.3%)	282 (38.0%)	718 (39.4%)
Past smoker	950 (25.5%)	40 (16.9%)	153 (27.9%)	52 (27.7%)	60 (32.6%)	189 (25.5%)	456 (25.0%)
Never smoker	1348 (36.2%)	138 (58.5%)	179 (32.7%)	54 (28.7%)	59 (32.1%)	271 (36.5%)	647 (35.5%)
Total cholesterol (mg/dl)	202.1 ± 47.6	202.7 ± 45.7	204.2 ± 48.0	192.8 ± 47.3	216.1 ± 51.5	200.8 ± 46.0	201.4 ± 47.6
LDL cholesterol (mg/dl)	117.4 ± 35.9	116.5 ± 33.5	112.9 ± 34.7	116.4 ± 35.7	120.9 ± 35.8	120.0 ± 36.8	117.4 ± 36.0
HDL cholesterol (mg/dl)	44.8 ± 15.0	47.4 ± 13.4	43.5 ± 14.4	39.8 ± 12.3	40.6 ± 15.0	42.7 ± 15.3	46.6 ± 15.1
Triglycerides (mg/dl)	230.0 ± 226.7	194.4 ± 185.8	279.1 ± 256.8	254.0 ± 305.5	318.2 ± 272.2	217.9 ± 175.8	213.6 ± 221.9
Total/HDL cholesterol	5.0 ± 2.4	4.6 ± 1.4	5.2 ± 2.5	5.2 ± 1.9	6.2 ± 3.3	5.2 ± 2.4	4.8 ± 2.3
BMI (kg/m^2)	25.7 ± 5.3	23.4 ± 3.8	25.6 ± 5.5	26.4 ± 5.6	25.5 ± 4.7	26.4 ± 5.3	25.8 ± 5.3
Heart rate (bpm)	69.5 ± 11.5	69.4 ± 10.6	68.0 ± 11.0	68.9 ± 11.6	68.7 ± 11.7	68.8 ± 11.7	70.3 ± 11.5
Prior CVD	136 (3.7%)	2 (0.8%)	18 (3.3%)	13 (6.9%)	4 (2.2%)	32 (4.3%)	67 (3.7%)
Diabetes	265 (7.1%)	6 (2.5%)	32 (5.8%)	16 (8.5%)	8 (4.3%)	64 (8.6%)	139 (7.6%)
Blood pressure-lowering drugs	700 (18.8%)	20 (8.5%)	87 (15.9%)	38 (20.2%)	34 (18.5%)	161 (21.7%)	360 (19.8%)
Lipid-lowering drugs	683 (18.4%)	23 (9.7%)	119 (21.7%)	47 (25.0%)	61 (33.2%)	134 (18.1%)	299 (16.4%)
Hepatitis B or C	584 (15.9%)	22 (9.3%)	87 (16.1%)	31 (16.8%)	30 (16.5%)	159 (21.6%)	255 (14.2%)
Baseline CD4 cell count (cells/μl)	677.8 ± 253.8	612.1 ± 224.4	654.7 ± 232.5	645.2 ± 225.5	659.7 ± 277.4	709.8 ± 265.4	685.5 ± 256.6
HIV-RNA (% ≥ 400 copies/ml)	3120 (84.1%)	216 (91.9%)	453 (82.8%)	159 (85.0%)	139 (76.0%)	559 (75.3%)	1594 (87.8%)
Duration of HIV (in years)	8.5 ± 4.9	7.7 ± 5.7	9.2 ± 5.1	9.8 ± 5.1	10.3 ± 4.6	8.9 ± 4.4	8.0 ± 4.8
Baseline NRTI regimen							

		Boosted protease inhibitors (*N* = 1156)					
	All population	**SQV/r**	**LPV/r**	**ATV/r**	**Other PI/r**	**Nonboosted PI**	**NNRTI – no PI**
	***N* = 3719**	***N* = 236**	***N* = 548**	***N* = 188**	***N* = 184**	***N* = 742**	***N* = 1821**
ZDV+3TC (without abacavir)	1446 (38.9%)	157 (66.5%)	142 (25.9%)	24 (12.8%)	38 (20.7%)	328 (44.2%)	757 (41.6%)
Tenofovir (without abacavir)	659 (17.7%)	20 (8.5%)	145 (26.5%)	93 (49.5%)	33 (17.9%)	45 (6.1%)	323 (17.7%)
Abacavir (without tenofovir)	549 (14.8%)	17 (7.2%)	109 (19.9%)	29 (15.4%)	35 (19.0%)	85 (11.5%)	274 (15.0%)
d4T+3TC	525 (14.1%)	14 (5.9%)	55 (10.0%)	4 (2.1%)	27 (14.7%)	155 (20.9%)	270 (14.8%)
Other NRTI regimens	540 (14.5%)	28 (11.9%)	97 (17.7%)	38 (20.2%)	51 (27.7%)	129 (17.4%)	197 (10.8%)

Mean ± SD or *N* (%). SQV/r, LPV/r, ATV/r, and PI/r means saquinavir, lopinavir, atazanavir, and other protease inhibitors boosted with ritonavir. 3TC, lamivudine; d4T, tavudine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; ZDV, zidovudine.

AIDS. Author manuscript; available in PMC 2012 January 28.

Table 2

Abnormal levels of QTc and PR interval.

		Boosted protease inhibitors					
	All population	**SQV/r**	**LPV/r**	**ATV/r**	**Other PI/r**	**Nonboosted PI**	**NNRTI – no PI**
QTcB (Bazett, ms)							
Number of participants with QTcB measurement	3304	212	449	154	148	625	1716
QTcB (mean ± SD)	415.4 ± 18.6	421.6 ± 19.3	412.7 ± 16.6	413.6 ± 16.6	414.7 ± 18.9	415.8 ± 20.0	415.4 ± 18.5
QTcB ≥ 440	318 (9.6%)	35 (16.5%)	27 (6.0%)	13 (8.4%)	10 (6.8%)	69 (11.0%)	164 (9.6%)
QTcB ≥ 460	81 (2.5%)	8 (3.8%)	4 (0.9%)	2 (1.3%)	4 (2.7%)	18 (2.9%)	45 (2.6%)
QTcB ≥ 440 in men or ≥ 460 in women	178 (5.4%)	13 (6.1%)	13 (2.9%)	7 (4.5%)	7 (4.7%)	41 (6.6%)	97 (5.7%)
QTcB ≥ 480	11 (0.3%)	1 (0.5%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	3 (0.5%)	6 (0.3%)
QTcB ≥ 500	4 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	3 (0.2%)
QTcF (Fredericia, ms)							
Number of participants with QTcF measurement	3304	212	449	154	148	625	1716
QTcF (mean ± SD)	406.2 ± 18.3	412.2 ± 18.1	404.8 ± 16.6	405.5 ± 17.4	406.2 ± 18.7	407.4 ± 20.0	405.6 ± 18.1
QTcF ≥ 440	140 (4.2%)	17 (8.0%)	12 (2.7%)	5 (3.2%)	6 (4.1%)	33 (5.3%)	67 (3.9%)
QTcF ≥ 460	22 (0.7%)	0 (0.0%)	3 (0.7%)	1 (0.6%)	0 (0.0%)	7 (1.1%)	11 (0.6%)
QTcF ≥ 440 ms in men or ≥ 460 ms in women	70 (2.1%)	4 (1.9%)	7 (1.6%)	3 (1.9%)	5 (3.4%)	16 (2.6%)	35 (2.0%)
QTcF ≥ 480 ms	4 (0.1%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	2 (0.1%)
QTcF ≥ 500 ms	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.1%)
PR duration (ms)							
Number of participants with PR measurement	3508	216	483	168	163	657	1821
PR duration (mean ± SD)	158.1 ± 23.2	158.0 ± 20.0	162.5 ± 24.2	163.4 ± 20.2	164.7 ± 36.8	159.7 ± 22.8	155.2 ± 21.6
PR duration l ≥ 200 ms	139 (4.0%)	6 (2.8%)	32 (6.6%)	9 (5.4%)	11 (6.7%)	30 (4.6%)	51 (2.8%)
PR duration ≥ 220 ms	49 (1.4%)	2 (0.9%)	13 (2.7%)	2 (1.2%)	5 (3.1%)	9 (1.4%)	18 (1.0%)
PR duration l ≥ 300 ms	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.2%)	0 (0.0%)	0 (0.0%)

Mean ± SD or *N* (%). SQV/r, LPV/r, ATV/r, and PI/r means saquinavir, lopinavir, atazanavir, and protease inhibitors boosted with ritonavir. NNRTI, nonnucleoside reverse transcriptase inhibitor.

Table 3

Baseline unadjusted and adjusted differences in QTc and PR interval duration for each of four protease inhibitor-based regimens versus an nonnucleoside reverse transcriptase inhibitor (no protease inhibitor)-based regimen.

	Model 1: unadjusted		Model 2: adjusted for model 1 and age, sex, race, and NRTI backbone regimen		Model 3: model 2 and smoking status, total cholesterol/HDL ratio, BMI, prior CVD, diabetes mellitus, blood pressure-lowering drugs, and lipid-lowering drugs		Model 4: model 3 and baseline duration of HIV infection, baseline CD4 cell count, and HIV-RNA	
	Coef. (SE)[a]	*P*	Coef. (SE)[a]	*P*	Coef. (SE)[a]	*P*	Coef. (SE)[a]	*P*
QTcB (Bazett)								
Any PI/r	− 0.73 (0.72)	0.31	− 1.51 (0.71)	0.03	− 1.47 (0.72)	0.04	− 1.53 (0.73)	0.04
SQV/r	5.43 (1.30)	<0.01	0.84 (1.58)	0.59	0.96 (1.59)	0.55	0.91 (1.60)	0.57
LPV/r	− 2.73 (0.93)	<0.01	− 2.55 (0.89)	<0.01	− 2.41 (0.90)	<0.01	− 2.46 (0.90)	<0.01
ATV/r	− 2.55 (1.48)	0.09	− 1.77 (1.43)	0.21	− 2.11 (1.46)	0.15	− 2.12 (1.47)	0.15
Other PI/r	− 1.19 (1.50)	0.43	− 0.08 (1.42)	0.96	− 0.09 (1.45)	0.95	− 0.16 (1.46)	0.91
Nonboosted PI	0.44 (0.83)	0.59	− 0.38 (0.79)	0.63	− 0.45 (0.80)	0.57	− 0.43 (0.81)	0.59
QTcF (Fredericia)								
Any PI/r	0.93 (0.71)	0.19	0.33 (0.70)	0.64	0.53 (0.71)	0.46	0.60 (0.72)	0.41
SQV/r	5.93 (1.28)	<0.01	2.72 (1.57)	0.08	2.50 (1.58)	0.11	2.60 (1.59)	0.10
LPV/r	− 0.51 (0.92)	0.58	− 0.42 (0.88)	0.64	− 0.22 (0.89)	0.81	− 0.15 (0.90)	0.87
ATV/r	− 1.10 (1.45)	0.45	− 0.75 (1.42)	0.59	− 0.37 (1.45)	0.80	− 0.27 (1.46)	0.86
Other PI/r	0.53 (1.47)	0.72	1.61 (1.41)	0.25	1.97 (1.44)	0.17	2.04 (1.45)	0.16
Nonboosted PI	1.91 (0.81)	0.02	1.32 (0.78)	0.09	1.62 (0.79)	0.04	1.81 (0.80)	0.02
PR interval[b]								
Any PI/r	5.74 (0.85)	<0.01	5.14 (0.87)	<0.01	5.12 (0.89)	<0.01	5.11 (0.90)	<0.01
SQV/r	2.24 (1.56)	0.15	1.54 (1.96)	0.43	1.91 (1.97)	0.33	1.66 (1.99)	0.40
LPV/r	6.18 (1.10)	<0.01	5.48 (1.09)	<0.01	5.58 (1.11)	<0.01	5.57 (1.11)	<0.01
ATV/r	6.47 (1.72)	<0.01	5.45 (1.73)	<0.01	5.08 (1.78)	<0.01	5.15 (1.78)	<0.01
Other PI/r	8.17 (1.74)	<0.01	6.76 (1.72)	<0.01	6.53 (1.76)	<0.01	6.60 (1.77)	<0.01
Nonboosted PI	3.78 (0.98)	<0.01	3.28 (0.98)	<0.01	2.90 (0.99)	<0.01	3.00 (1.00)	<0.01

SQV/r, LPV/r, ATV/r, and PI/r means saquinavir, lopinavir, atazanavir, and protease inhibitors boosted with ritonavir. CVD, cardiovascular disease; HDL, high-density lipoprotein; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

[a] NNRTI use (no protease inhibitors) is the reference value in all models (i.e., all differences cited are from those taking an NNRTI regimen).

[b] Additionally adjusted for heart rate.

AIDS. Author manuscript; available in PMC 2012 January 28.

Table 4

Change in baseline QT duration and PR interval after 12 months of continuous versus interrupted antiretroviral use.

	Drug conservation group				Viral suppression group				
	N[a]	Baseline Mean (SD)	Change (M12-BL) Mean (SD)	*P***	*N*[a]	Baseline Mean (SD)	Change (M12-BL) Mean (SD)	*P***	*P****
QTcB (Bazett)									
Any PI/r	116	411.2 (17.78)	0.05 (16.49)	0.97	339	416.9 (18.54)	0.02 (18.01)	0.98	0.48
SQV/r	17	407.4 (18.28)	2.46 (19.84)	0.62	91	422.0 (19.88)	− 0.69 (19.26)	0.73	0.43
LPV/r	60	410.7 (17.45)	0.73 (15.47)	0.72	124	415.0 (17.17)	− 0.00 (16.76)	>0.99	0.85
Other PI/r[b]	39	413.7 (18.15)	− 2.05 (16.67)	0.45	82	414.7 (18.89)	− 0.22 (18.62)	0.92	0.87
Nonboosted PI	127	415.2 (19.02)	1.23 (18.72)	0.46	169	416.3 (22.03)	2.15 (19.52)	0.15	0.28
QTcF (Fredericia)									
Any PI/r	116	404.0 (19.31)	− 3.27 (16.29)	0.03	339	408.7 (18.00)	− 0.05 (17.82)	0.96	0.04
SQV/r	17	401.6 (22.54)	− 0.61 (18.24)	0.89	91	412.9 (17.95)	− 0.40 (18.62)	0.84	0.56
LPV/r	60	403.6 (19.23)	− 2.98 (14.79)	0.12	124	407.0 (18.23)	0.87 (16.47)	0.56	0.16
Other PI/r[b]	39	405.7 (18.31)	− 4.89 (17.81)	0.09	82	407.9 (18.72)	− 1.85 (18.82)	0.38	0.39
Nonboosted PI	127	405.7 (18.36)	− 1.31 (18.31)	0.42	169	407.6 (19.07)	1.56 (17.78)	0.26	0.04
PR interval									
Any PI/r	136	160.4 (21.18)	− 2.45 (12.10)	0.02	396	162.8 (24.40)	− 1.59 (16.90)	0.06	0.72
SQV/r	17	164.5 (25.64)	− 2.82 (16.91)	0.50	97	156.3 (19.52)	− 1.09 (12.60)	0.40	0.26
LPV/r	76	160.6 (20.64)	− 2.54 (11.55)	0.06	143	164.7 (28.85)	− 0.42 (15.60)	0.75	0.75
Other PI/r[b]	43	158.3 (20.49)	− 2.14 (11.12)	0.21	106	163.6 (21.46)	− 2.30 (22.64)	0.30	0.68
Nonboosted PI	141	161.3 (21.91)	− 2.75 (11.67)	<0.01	191	161.5 (24.41)	− 0.86 (14.54)	0.42	0.23

SQV/r, LPV/r, and PI/r means saquinavir, lopinavir, and other protease inhibitors boosted with ritonavir. BL, baseline; M12, month 12; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

[a] All participants have both baseline and month-12 ECGs and had not either reinitiated antiretroviral therapy (ART; drug conservation group) or changed their treatment regimen (viral suppression group) through the 12-month period.

[b] Including atazanavir boosted with ritonavir.

** *P* value obtained from paired *t*-test comparing baseline and month-12 mean values of PR and QT.

*** *P* value for comparison between mean changes in the drug conservation group versus viral suppression group after adjusting for baseline value, age, sex, race, smoking status, total cholesterol/high-density lipoprotein (HDL) ratio, body mass index (BMI), prior cardiovascular disease (CVD), diabetes, use of blood pressure-lowering drugs, use of lipid-lowering drugs, duration of HIV infection, and baseline CD4 cell count and HIV-RNA levels (and heart rate in the PR models). These drug conservation-viral suppression comparisons are not protected by randomization.

Table 5

Change in baseline QTc and PR interval durations after 24 months of continuous versus interrupted antiretroviral use.

	Drug conservation group				Vital suppression group				
	N^a	Baseline Mean (SD)	Change (M24-BL) Mean (SD)	P^{**}	N^a	Baseline Mean (SD)	Change (M24-BL) Mean (SD)	P^{**}	P^{***}
QTcB (Bazett)									
Any PI/r	40	412.4 (20.59)	− 1.88 (15.98)	0.46	165	415.9 (16.60)	− 0.02 (16.28)	0.99	0.36
SQV/r	5	407.6 (28.26)	− 1.72 (12.07)	0.77	11	419.5 (13.34)	5.15 (7.89)	0.06	0.44
LPV/r	22	410.8 (21.64)	0.30 (19.17)	0.94	79	415.5 (16.25)	− 0.64 (17.67)	0.75	0.97
Other PI/r[b]	13	416.8 (16.04)	− 5.65 (10.68)	0.08	38	414.8 (19.15)	− 0.42 (18.50)	0.89	0.54
Nonboosted PI	58	415.8 (18.00)	− 0.94 (16.03)	0.66	81	414.1 (18.98)	2.43 (17.86)	0.22	0.18
QTcF (Fredericia)									
Any PI/r	40	405.8 (21.23)	− 7.79 (18.77)	0.01	165	407.2 (16.32)	0.25 (16.28)	0.85	<0.01
SQV/r	5	398.0 (23.70)	− 9.90 (7.76)	0.05	11	411.3 (19.41)	6.54 (12.34)	0.11	0.38
LPV/r	22	402.2 (18.91)	− 4.10 (21.76)	0.39	79	406.4 (16.13)	0.32 (17.01)	0.87	0.25
Other PI/r[b]	13	414.8 (22.69)	− 13.2 (15.42)	0.009	38	407.8 (19.14)	− 2.37 (16.95)	0.39	0.06
Nonboosted PI	58	405.7 (17.65)	− 2.97 (15.13)	0.14	81	405.5 (18.82)	2.80 (18.24)	0.17	0.03
PR interval									
Any PI/r	47	159.9 (17.60)	− 7.38 (12.21)	<0.001	194	163.8 (26.31)	0.53 (14.35)	0.61	<0.01
SQV/r	6	165.7 (15.62)	− 12.7 (10.93)	0.04	13	157.4 (22.08)	6.15 (23.42)	0.36	0.15
LPV/r	26	161.8 (16.90)	− 6.96 (10.93)	0.003	88	165.0 (30.12)	1.32 (13.99)	0.38	0.01
Other PI/r[b]	15	154.3 (19.14)	− 6.00 (14.81)	0.14	49	161.5 (22.27)	− 0.18 (12.61)	0.92	0.11
Nonboosted PI	68	163.4 (21.28)	− 4.04 (21.21)	0.12	99	162.0 (26.50)	− 0.66 (15.49)	0.67	0.43

SQV/r, LPV/r, ATV/r, and PI/r means saquinavir, lopinavir, atazanavir and other protease inhibitors boosted with ritonavir. BL, baseline; M24, month 24; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

[a] All participants have both baseline and month-24 ECGs and had not either reinitiated ART (drug conservation group) or change their treatment regimen (viral suppression group) through the 24-month period.

[**] *P* value obtained from paired *t*-test comparing baseline and month-24 mean values of PR and QT.

[***] *P* value for comparison between mean changes in the drug conservation group versus viral suppression group after adjusting for baseline value, age, sex, race, smoking status, total cholesterol/HDL ratio, BMI, prior cardiovascular disease (CVD), diabetes, use of blood pressure-lowering drugs, use of lipid-lowering drugs, duration of HIV infection, and baseline CD4 cell count and HIV-RNA levels (and heart rate in the PR models).

[b] Including atazanavir boosted with ritonavir.