Poster No. H-218

50th ICAAC 2010

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Associations between Protease Inhibitors (PIs) and QTc and PR Interval Durations in the Strategies for Management of Antiretroviral Therapy (SMART) Trial

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BACKGROUND

There are contradictory reports – based on case series and single site studies - regarding the effects of protease inhibitors (PIs) on the electrocardiographic (ECG) measures of QT and PR interval durations. The effect of interrupting use of PIs on QT and PR progression is also unknown. The SMART study, with its large sample size, standardized ECG collection methodology and centrally automated ECG reading, serves as a unique source of data to asses whether use of PIs (compared with NNRTIs) is associated with these ECG abnormalities, and whether interruption of Antiretroviral Therapy (ART) reverses them.

METHODS

This analysis included 3,719 participants from the SMART study, of whom 1,879 were randomised to receive intermittent antiretroviral therapy [drug conservation (DC) group], while the rest received these drugs continuously [viral suppression (VS) group](**Figure 1**). Linear regression analysis was used to compare four boosted PI regimens (SQV/r, LPV/r, ATV/r, and other PI/r), and non-boosted PI regimens with NNRTI (no PI) regimens for Bazett's (QTcB) and Fridericia's (QTcF) heart rate corrected QT and PR. Changes in QTcB, QTcF and PR after 12 and 24 months of randomisation were compared in the DC group and VS group.

RESULTS

Table 1 shows baseline characteristics stratified by ART use. Average levels of QTcB, QTcF, and PR duration at entry were 415, 406, and 158 ms (**Table 2**). At study entry, 49% of participants were taking an NNRTI (no PI)-based regimen and 31% were prescribed a boosted PI (PI/r), the most common being lopinavir (LPV/r). After adjustment for baseline factors, QTcB and QTcF levels did not vary by boosted PI group (p=0.26 and p=0.34, respectively). For those given any of the boosted PIs, QTcB was 1.5 ms lower than the NNRTI group (p=0.04) (**Table 3**). Both boosted and non-boosted PI-containing regimens were significantly associated (p<0.01 for each) with longer PR intervals compared to the NNRTI group (**Table 3**). After adjustment, the difference between boosted PIs and the NNRTI group was 5.11 ms (p<0.01); for non-boosted PIs, this difference was 3.00 ms (p<0.01) (**Table 3**). Following ART interruption, PR duration declined for both the boosted and non-boosted PI groups and compared to the VS group, significant changes in PR interval were observed 24 months after ART interruption of boosted PIs (p<0.01) (**Table 4**).

CONCLUSIONS

Different PI-based regimens have a similar, minimal effect on QT compared to NNRTI-based regimens. All PI-based regimens (boosted and non-boosted) were associated with prolongation of PR, and interruption of PI regimens reduced the prolonged PR duration. Further studies are needed to confirm the findings of this study, preferably using a randomised study design.

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

Figure 1

Study Flow Diagram

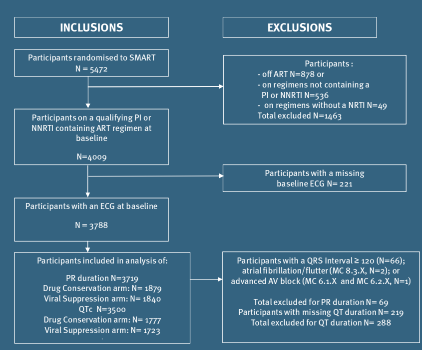

Table 1

Baseline characteristics stratified by the baseline antiretroviral use; Mean+ SD or N (%)

	All population N=3719	Boosted protease inhibitors (N=1156) SQV/r N=236	LPV/r N=548	ATV/r N=188	Other PI/r N=184	Non-boosted PI N=742	NNRTI – no PI 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
Gender (% 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 ($cells/mm^3$)	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							
ATV+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%)

SQV/r, LPV/r, ATV/r, and PI/r = Saquinavir, Lopinavir, Atazanavir and other Protease Inhibitors boosted with Ritonavir; NNRTI = Non-nucleoside Reverse Transcriptase Inhibitor; NRTI = Nucleoside Reverse Transcriptase Inhibitor

Table 2

Abnormal levels of QTc and PR Interval; Mean+ SD or N (%)

	All population	Boosted protease inhibitors SQV/r	LPV/r	ATV/r	Other PI/r	Non-boosted 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 males or ≥ 460 in females	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 (Fridericia, 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 males or ≥ 460 ms in females	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 ≥ 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 ≥ 300 ms	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.2%)	0 (0.0%)	0 (0.0%)

SQV/r, LPV/r, ATV/r, and PI/r = Saquinavir, Lopinavir, Atazanavir and Proteas Inhibitors boosted with Ritonavir; NNRTI = Non-nucleoside Reverse Transcriptase Inhibitor

Table 3

Baseline unadjusted and adjusted differences in QTc and PR interval duration for each of four PI-based regimens versus an NNRTI (no PI)-based regimen

	Model 1: unadjusted		Model 2: adjusted for Model 1 plus age, gender, race, and NRTI backbone regimen		Model 3: Model 2 plus smoking status, total cholesterol/ HDL ratio, BMI, prior CVD, diabetes mellitus, blood pressure-lowering drugs, and lipid-lowering drugs		Model 4: Model 3 plus baseline duration of HIV infection, baseline CD4 and HIV-RNA	
	Coef. (SE)*	p	Coef. (SE)*	p	Coef. (SE)*	p	Coef. (SE)*	p
QTcB (Bazett)								
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
Non-boosted 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
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
QTcF (Fridericia)								
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
Non-boosted 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
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
PR Interval**								
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
Non-boosted 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
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, LPV/r, ATV/r, and PI/r = Saquinavir, Lopinavir, Atazanavir and Protease Inhibitors boosted with Ritonavir; NNRTI = Non-nucleoside Reverse Transcriptase Inhibitor; NRTI = Nucleoside Reverse Transcriptase Inhibitor
*Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) use (No Protease inhibitors) is the reference value in all models
** Additionally adjusted for heart rate

Table 4

Change in baseline QTc and PR interval durations after 12 and 24 months of continuous versus interrupted antiretroviral use

		DC Group N*	Baseline Mean (SD)	Change (M12-BL & M24-BL) Mean (SD)	p**	VS Group N*	Baseline Mean (SD)	Change (M12-BL & M24-BL) Mean (SD)	p**	p***
QTcB (Bazett)										
SQV/r	12m	17	407.4 (18.28)	2.46 (19.84)	0.62	91	422.0 (19.88)	-0.69 (19.26)	0.73	0.43
	24m	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	12m	60	410.7 (17.45)	0.73 (15.47)	0.72	124	415.0 (17.17)	-0.00 (16.76)	>0.99	0.85
	24m	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§	12m	39	413.7 (18.15)	-2.05 (16.67)	0.45	82	414.7 (18.89)	-0.22 (18.62)	0.92	0.87
	24m	13	416.8 (16.04)	-5.65 (10.68)	0.08	38	414.8 (19.15)	-0.42 (18.50)	0.89	0.54
Non-boosted PI	12m	127	415.2 (19.02)	1.23 (18.72)	0.46	169	416.3 (22.03)	2.15 (19.52)	0.15	0.28
	24m	58	415.8 (18.00)	-0.94 (16.03)	0.66	81	414.1 (18.98)	2.43 (17.86)	0.22	0.18
Any PI/r	12m	116	411.2 (17.78)	0.05 (16.49)	0.97	339	416.9 (18.54)	0.02 (18.01)	0.98	0.48
	24m	40	412.4 (20.59)	-1.88 (15.98)	0.46	165	415.9 (16.60)	-0.02 (16.28)	0.99	0.36
QTcF (Fridericia)										
SQV/r	12m	17	401.6 (22.54)	-0.61 (18.24)	0.89	91	412.9 (17.95)	-0.40 (18.62)	0.84	0.56
	24m	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	12m	60	403.6 (19.23)	-2.98 (14.79)	0.12	124	407.0 (18.23)	0.87 (16.47)	0.56	0.16
	24m	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§	12m	39	405.7 (18.31)	-4.89 (17.81)	0.09	82	407.9 (18.72)	-1.85 (18.82)	0.38	0.39
	24m	13	414.8 (22.69)	-13.2 (15.42)	<0.01	38	407.8 (19.14)	-2.37 (16.95)	0.39	0.06
Non-boosted PI	12m	127	405.7 (18.36)	-1.31 (18.31)	0.42	169	407.6 (19.07)	1.56 (17.78)	0.26	0.04
	24m	58	405.7 (17.65)	-2.97 (15.13)	0.14	81	405.5 (18.82)	2.80 (18.24)	0.17	0.03
Any PI/r	12m	116	404.0 (19.31)	-3.27 (16.29)	0.03	339	408.7 (18.00)	-0.05 (17.82)	0.96	0.04
	24m	40	405.8 (21.23)	-7.79 (18.77)	0.01	165	407.2 (16.32)	0.25 (16.28)	0.85	<0.01
PR Interval										
SQV/r	12m	17	164.5 (25.64)	-2.82 (16.91)	0.50	97	156.3 (19.52)	-1.09 (12.60)	0.40	0.26
	24m	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	12m	76	160.6 (20.64)	-2.54 (11.55)	0.06	143	164.7 (28.85)	-0.42 (15.60)	0.75	0.75
	24m	26	161.8 (16.90)	-6.96 (10.93)	<0.01	88	165.0 (30.12)	1.32 (13.99)	0.38	0.01
Other PI/r§	12m	43	158.3 (20.49)	-2.14 (11.12)	0.21	106	163.6 (21.46)	-2.30 (22.64)	0.30	0.68
	24m	15	154.3 (19.14)	-6.00 (14.81)	0.14	49	161.5 (22.27)	-0.18 (12.61)	0.92	0.11
Non-boosted PI	12m	141	161.3 (21.91)	-2.75 (11.67)	<0.01	191	161.5 (24.41)	-0.86 (14.54)	0.42	0.23
	24m	68	163.4 (21.28)	-4.04 (21.21)	0.12	99	162.0 (26.50)	-0.66 (15.49)	0.67	0.43
Any PI/r	12m	136	160.4 (21.18)	-2.45 (12.10)	0.02	396	162.8 (24.40)	-1.59 (16.90)	0.06	0.72
	24m	47	159.9 (17.60)	-7.38 (12.21)	<0.01	194	163.8 (26.31)	0.53 (14.35)	0.61	<0.01

SQV/r, LPV/r, and PI/r = Saquinavir, Lopinavir, other Protease Inhibitors boosted with Ritonavir; NNRTI = Non-nucleoside Reverse Transcriptase Inhibitor; NRTI = Nucleoside Reverse Transcriptase Inhibitor
*All participants have both baseline and month-12 or month-24 ECGs and had not either reinitiated ART (DC group) or changed their treatment regimen (VS group) thorough the 24-month period
** p-value obtained from paired T test comparing baseline and month-12 or month -24 mean values of PR and QTc
*** p-value for comparison between mean changes in the DC group versus VS group after adjusting for baseline value, age, gender, race, smoking status, total cholesterol/HDL ratio, BMI, prior CVD, diabetes, use of blood pressure lowering drugs, use of lipid lowering drugs, duration of HIV infection, and baseline CD4 and HIV-RNA (plus heart rate in the PR models)
§ Including atazanavir boosted with ritonavir

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