TITLE PAGE: CONCISE COMMUNICATION

Prevalence and risk factors of prolonged QT interval and electrocardiographic abnormalities in persons living with HIV

Running head: "Prolonged QTc and electrocardiographic abnormalities in HIV infection"

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Abnormal electrocardiograms (ECG) are associated with increased risk of arrhythmias and sudden cardiac death. We aimed to investigate the prevalence and associated risk factors of prolonged QTc and major ECG abnormalities, in persons living with HIV (PLWH) and uninfected controls.

DESIGN

PLWH aged ≥40 were recruited from the Copenhagen comorbidity in HIV infection (COCOMO) study and matched on sex and age to uninfected controls from the Copenhagen General Population Study.

METHODS

ECGs were categorized according to Minnesota Code Manual of ECG Findings definition of major abnormalities. A QT interval corrected for heart rate (QTc) >440ms in males and >460ms in females was considered prolonged. Pathologic Q-waves were defined as presence of major Q-wave abnormalities.

RESULTS

ECGs were available for 745 PLWH and 2,977 controls. Prolonged QTc was prevalent in 9% of PLWH and 6% of controls, p=.052. Pathologic Q-waves were more common in PLWH (6%) than in controls (4%), p=.028. There was no difference in prevalence of major ECG abnormalities between PLWH and controls, p=.987.

In adjusted analyses, HIV was associated with a 3.6ms[1.8-5.4] longer QTc interval, *p*<.001, and HIV was independently associated with prolonged QTc (adjusted odds ratio: 1.59 [1.14-2.19]), p=.005. HIV was borderline associated to pathologic Q-waves after adjusting, p=.051.

CONCLUSION

HIV was associated with higher odds ratio of prolonged QTc after adjustment for cardiovascular risk factors, but analyses were not adjusted for QT-prolonging medication. Although evidence indicated more pathologic Q-waves in PLWH, the risk seemed to be associated mainly with an adverse risk profile.

Keywords HIV; ECG; EKG; QT interval; Abnormalities; Cardiovascular disease; Comorbidities

BACKGROUND

Previously, major electrocardiographic (ECG) abnormalities, including atrial fibrillation (AF), have been shown to be both prevalent and to carry a poor prognosis in persons living with HIV (PLWH)[1–3]. Similarly, prolonged corrected QT interval (QTc) is common among PLWH and associated with malignant arrhythmias and sudden cardiac death (SCD)[4], but few studies have compared the prevalence of prolonged QTc in PLWH and the uninfected population[5,6]. Previous studies have included treatment naïve patients, patients from high risk populations, and patients with advanced HIV disease[5–8]. Thus, the effects of HIV on QTc may be confounded by an adverse risk profile with excess smoking, inflammation, and comorbidity (e.g structural heart disease) among PLWH[9–13]. Furthermore, use of QT-prolonging drugs may differ in PLWH[14]. Thus, to describe the effect of HIV infection on ECG abnormalities and prolonged QTc, a well-characterized population of PLWH and comparable uninfected controls is needed.

We aimed to determine the prevalence and associated risk factors of prolonged QTc and major electrocardiographic abnormalities among well-treated PLWH and uninfected controls and to determine if HIV is independently associated with prolonged QTc and/or major electrocardiographic abnormalities in PLWH. We hypothesized that HIV would be independently associated with prolonged QTc and major ECG abnormalities.

METHODS

Study populations and demographics

PLWH were recruited from the Copenhagen Co-morbidity in HIV Infection (COCOMO) Study (NCT02382822). The COCOMO study is a non-interventional cohort study which assess the burden and pathogenesis of non-AIDS comorbidities in PLWH. The procedures for recruitment and data collection have been described elsewhere[9].

Uninfected controls were included from the Copenhagen General Population Study (CGPS), a non-interventional general population study[15]. All participants in COCOMO and a subset of CGPS participants older than 40 years of age had an electronic ECG recorded. COCOMO participants older than 40 were frequency matched by age and sex (1:4) to participants from CGPS.

Identical questionnaires were used to collect information regarding medical history, smoking, alcohol consumption and use of medication. A physical exam including anthropometrics and blood pressure was performed by trained clinical staff. Measurements of high-sensitivity C-reactive protein (hsCRP), LDL cholesterol (LDL) and glucose were done[16]. HIV-related characteristics were obtained through review of medical records.

We defined hypertension as current anti-hypertensive treatment and/or systolic ≥140mmHg and/or diastolic blood pressure ≥90mmHg[9]. Body Mass Index (BMI) was defined according to the WHO classification[17] and dyslipidemia was defined as LDL ≥160mg/dl (4.14mM) and/or current lipid lowering treatment[9].

ECG recording

ECGs were recorded by trained using a CardioSoft electrocardiograph Module and CardioSoft v6.7 Diagnostic System (GE Healthcare) software.

A resting ECG was only recorded and stored when all lead readings were calibrated, and no muscular interference was visible. Recorded ECGs were transferred to the MUSE Cardiology Information System (GE Healthcare, Wauwatosa, WI) in standard 12SL output format.

ECG variables

ECGs were coded according to the Minnesota code manual for electrocardiographic findings (MC)[18]. AF, atrioventricular (AV) conduction abnormalities and length of intervals and

segments were coded using v.21 of the validated Marquette 12SL algorithm[4]. We prespecified to use Bazett's formula for QT interval correction. QT prolongation was defined as QTc >460ms for women and as QTc >450ms for men. Major prolongation was defined as QTc >480ms for both women and men[19]. Participants with a QRS duration of 120ms or more or with ventricular rates >100bpm, were not included in the analyses of the QT interval.

Electrocardiographic abnormalities were classified as major abnormalities as suggested by MC and according to similar studies[6,20](MC criteria in supplementary table 1 , http://links.lww.com/QAD/B517). All ECGs with major MC abnormalities were manually overread by a physician blinded to HIV status. Manually inspected ECGs of poor quality were excluded.

Statistics

Student's t tests or Mann–Whitney U tests were used for comparison of continuous data and χ2 tests or Fisher's exact test were used for categorical data.

We assessed whether HIV was associated with prolonged QTc or major MC abnormalities using multivariable logistic regression analyses adjusted for a prespecified model. The model included age, sex, hypertension, diabetes, dyslipidemia and smoking status. We further tested if prespecified major MC abnormalities 1) pathologic Q-waves; 2) intraventricular blocks (IV-blocks); 3) AF were associated with HIV or other independent variables. We investigated the association of HIV and independent variables to QTc length in multiple linear regression adjusted for the same prespecified model. Within PLWH, we tested whether HIV-related characteristics including current cART use (protease inhibitors, Efavirenz and Rilpivirine) were associated with prolonged QTc or major MC abnormalities.

A *P*-value .05 inferred statistical significance. All analyses were generated as available case analysis using SAS software v9.4 (SAS Institute, USA.)

RESULTS

Of 3,735 coded ECGs, 484 met an MC criterion for major abnormality. On manual overreading of these, 13 (2%) were excluded due to inadequate quality and 32 (7%) were reclassified as *no abnormality*. ECGs were available for 745 PLWH and 2,977 controls (Supplementary Figure 1, http://links.lww.com/QAD/B517).

Patient characteristics are listed in Table 1.

Prolonged QTc among PLWH and uninfected controls

In PLWH and controls, mean QTc was 422ms (95% confidence interval[CI]: [421-424] and 421ms [420-421], respectively, *p*=.049 (Fig. 2). After adjusting, HIV was associated with 3.6ms [1.8-5.4] longer QTc interval, *p*<.001. Furthermore, age, female sex, hypertension, smoking, diabetes, obesity and hsCRP were associated with longer QTc (table 2).

Prolonged QTc was found in 9% of PLWH and in 6% of the controls, *p* =.052, corresponding to a crude odds ratio (OR) of 1.35 [1.00-1.83]. Major prolongation of the QTc was present in 1.3% of PLWH and 0.5% of controls, *p*=.021, but was not associated with HIV in adjusted analyses, *p*=.168 (Supplementary Figure 2, http://links.lww.com/QAD/B517).

After adjusting, HIV was independently associated with prolonged QTc with an adjusted odds ratio (aOR) of 1.59 [1.14-2.19], *p*=.005. Furthermore, older age, hypertension, and pathologic Q-waves were associated with prolonged QTc (table 2).

Prolonged QTc among PLWH

In analyses restricted to PLWH, current CD4, CD4 nadir <200, CD8, CD4:CD8 ratio, previous AIDS defining condition, current use of protease inhibitor, Efavirenz or Rilpivirine, and illicit drug use were not independently associated with prolonged QTc.

Major abnormalities among PLWH and uninfected controls

A major MC abnormality was present in 88 (12%) of PLWH and in 351 (12%) of controls, *p*=.987. Pathologic Q-waves were found in 45 (6%) and 124 (4%) of PLWH and controls, respectively, corresponding to a crude odds ratio (OR) of 1.48 [1.04-2.10], *p*=.028. There was no difference in prevalence of IV-block *p*=.839, or AF *p*=.285, (Supplementary Table 2, http://links.lww.com/QAD/B517).

HIV was not independently associated with major MC abnormalities when adjusted for confounders, *p*=.141, or with any specific major MC abnormality, including AF (*p*=.254) or IV-blocks (*p*=.723). However, a borderline association with pathologic Q-waves was found (p=.051). In PLWH, but not controls, pathologic Q-waves were also associated with hsCRP (aOR per 10 mg/L increase: 1.36 [1.02-1.83]).

Discussion

PWLH had a higher prevalence of prolonged QTc compared to uninfected controls, and HIV was independently associated with prolonged QTc after adjusting for traditional risk factors, though we did not adjust for use of QT prolonging medications. cART regimen was not associated with prolonged QTc. Prevalence of pathologic Q-waves was higher among PLWH, but the association was attenuated when adjusting for traditional risk factors, suggesting that traditional risks may carry some of the excess risk.

Prolonged QTc is independently associated with malignant ventricular arrhythmias and SCD[4], and has been reported to be higher among PLWH in both treatment naïve[8] and patients on cART[14,21]. Prevalence estimates differ markedly and ranges from 5% to more than 40%, depending on the investigated population. Most prior studies are limited by size, have lacked comparable controls or have recruited patients from highly selected populations[8,14,21–23]. In the HIV-HEART study, prolonged QTc was present in 21% among PLWH vs 3.5% among

the uninfected[14]. In the MACS cohort, there was no difference in prevalence of prolonged QTc between PLWH and controls (3% in both groups), but the QTc interval was 4ms longer among PLWH when adjusting for confounders[21]. The association was attenuated by adjustment for inflammatory markers. The prevalence of prolonged QTc in our study was 9% and in between the estimates from the HIV-HEART and MACS cohorts and our data confirm the association between inflammation and QTc in other studies[11,21]. hsCRP is, however, a crude marker of inflammation and further studies should explore the impact of different inflammatory pathways in PLWH and uninfected.

We expected major MC abnormalities to be prevalent among PLWH and while more than one in ten PLWH did have major MC abnormalities, prevalence was not higher than among the controls, as anticipated by prior studies without controls[2,6]. HIV and pathologic Q-waves were associated in univariable analyses, but this association was attenuated to borderline significance after adjusting for traditional risk factors, suggesting an adverse risk profile among PLWH[9,24] to contribute. PLWH have increased risk of heart failure and cardiomyopathies[12], and studies of intraventricular conduction defects in PLWH have found QRS-duration to be associated with use of protease inhibitors[25]. We therefore hypothesized HIV infection to be associated with IV-block, but distribution of IV-blocks was similar in PLWH and controls and there was no association to specific cART regimens. A recent analysis of five thousand PLWH did not report AF to be more prevalent than in controls, but found low CD4 nadir to be predictive of AF[3]. In an indirect comparison to the Framingham study, a study found higher incidence of AF in PLWH aged 55-75, but they did not account for differences in risk factors[2]. We found a low (1%) prevalence of AF in PLWH and controls and comparable to participants in Framingham[26]. The few cases did not allow us to investigate associations between AF and CD4 nadir.

Common causes of acquired QTc prolongation include use of methadone and antiarrhythmic, antibiotic, and psychotropic medications which may all be more commonly used among PLWH[27,28]. Limitations to the study, thus, included inability to adjust for QT prolonging medication use, and although MC criteria are validated against clinical outcomes, other categorizations may have produced different estimates of abnormalities. However, ECGs were recorded on the same device and grouped according to the same criteria, interval and segment lengths were automatically measured and all ECG evaluations were blinded to HIV status. Thus, a different categorization would likely have affected both populations equally. Additionally, the cross-sectional design prevents us from drawing conclusions regarding causality. Strengths of the study include the size and the uniform approach to data collection.

In conclusion, well-treated PLWH had a higher prevalence of prolonged QTc and pathologic Q-waves and ECG evidence of previous myocardial infarction than uninfected controls. Adjusting for risk factors attenuated the association between HIV and pathologic Q-waves, but HIV was *independently* associated with prolonged QTc. hsCRP was marginally associated with QTc length and pathologic Q-waves (but not prolonged QTc) in PLWH. Further studies are needed to explore the impact of prolonged QTc on clinical outcomes in PLWH.

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Table 1. Demographic characteristics of persons living with HIV and uninfected controls

Demographic characteristics		
	PLWH 745	**Controls 2,977**
Men, n (%)	641 (86)	2,481 (83)
Age, mean (SD)	54 (9)	56 (9)
Origin		
• Scandinavian	571 (77)	2,782 (93)
• Other European	78 (11)	130 (4)
• Middle East and Indian subcontinent	12 (2)	19 (1)
• Other	82 (11)	9 (0.3)
Smoking status, n (%)		
• Current	195 (26)	365 (12)
• Former	292 (39)	1,284 (43)
• Never	257 (35)	1,303 (44)
Pack years median (IQR)	20 (7-34)	13 (3-26)
Hypertension, n (%)	348 (47)	1,861 (63)
Diabetes, n (%)	37 (5)	123 (4)
Obese (BMI>30)	73 (10)	538 (18)
LDL	2.8 (1)	3.2 (1)
Statin	120 (16)	388 (13)
Dyslipidemia	71 (10)	473 (16)
HIV specific characteristics		
Mode of transmission		
• MSM	520 (70)	-
• Heterosexual	161 (22)	-
• IDU	8 (1.1)	-
• Other or unknown	56 (7.5)	-
Current CD4 count, CD4/μL, median (IQR)	510 (670-870)	-
• <200 CD4/μL, n (%)	11 (1.5)	-
• 200–349 CD4/μL, n (%)	45 (6.0)	-
• 350-499 CD4/μL, n (%)	109 (15)	-
• >500 CD4/μL, n (%)	572 (77)	-
CD4 nadir <200/μL, n (%)	327 (44)	-
HIV RNA <50 copies/mL, n (%)	706 (95)	-
Current cART use, n (%)	732 (98)	-
• Rilpivirine use, n (%)	16 (2.3)	-
• Efavirenz use, n (%)	217 (30)	-
• Protease inhibitor use, n (%)	222 (30)	-
IDU: Injecting drug use; MSM:Men who have sex with men; Number of missing data per variable: Origin: 39; Smoking status:26; Hypertension:48; Diabetes:23; Obese:7; Dyslipidemia:127		

Table 2. Association of corrected QT interval to independent risk factors.

Association of corrected QT interval to independent risk factors ※							
	QTc length				Prolonged QTc			
	β-coefficient	P	Adjusted β-coefficient	P	OR	P	aOR	P
HIV yes *vs.* no	1.9 [0.0-3.7]	.049	3.6 [1.8-5.4]	<.001	1.35 [1.00-1.83]	.052	1.59 [1.14 2.19]	.005
Age*	3.0 [2.3-3.7]	<.001	2.9[2.1-3.7]	<.001	1.54 [1.34-1.77]	<.001	1.45 [1.25-1.67]	<.001
Male sex	-8.3 [-10.2-(-)6.5]	<.001	-11.2 [-13.1-(-)9.2]	<.001	1.03 [0.72-1.46]	.888	0.72 [0.51-1.06]	.086
Hypertension	6.0 [4.6-7.4]	<.001	5.8 [4.3-7.3]	<.001	2.34 [1.72-3.18]	<.001	1.94 [1.41 2.71]	<.001
Current smoker	1.6 [-0.4-3.5]	.114	2.6 [0.6-4.5]	.010	1.14 [0.81-1.62]	.453	1.26 [0.87-1.79]	.212
Dyslipidemia	1.1 [-0.9-3.1]	.297	1.4 [-0.5-3.4]	.149	1.12 [0.78-1.60]	.541	1.18 [0.81-1.68]	.368
Diabetes	1.4 [0.74-2.76]	.289	4.4 [0.9-8.0]	.014	2.01 [1.20-3.35]	.007	1.60 [0.91-2.66]	.086
hsCRP**	2.3 [0.8-3.9]	.002	1.5 [0.02-3.0]	.046	1.14 [0.90-1.36]	.196	1.07 [0.82-1.29]	.507
Heavy Drinker¥	1.6 [0.1-3.2]	.040	1.0 [-0.6-2.6]	.227	1.17 [0.89-1.55]	.263	0.94 [0.70 1.27]	.702
Obesity¥¥	4.6 [2.7-6.5]	<.001	3.0 [1.1-5.0]	.002	1.43 [1.04-1.98]	.027	1.21 [0.85-1.68]	.287
Pathologic Q-waves	6.9 [3.3-10.5]	.001	5.6 [2.0-9.3]	.002	2.66 [1.66-4.28]	<.001	2.24 [1.33-3.64]	.002
Scandinavian (yes vs. no)	5.3 [2.6-8.0]	<.001	3.4 [0.7-6.0]	.014	1.49 [0.90-2.47]	.122	1.30 [0.80-2.25]	.317
※ *Multiple linear regression analyses (left panel) and multivariable logistic analyses (right panel) with 95% confidence intervals. Model Adjusted for Age, Sex, Hypertension, Smoking status, Dyslipidemia and Diabetes.* *per decade older **per 10 mg/L increase ¥defined as 14 or more units of alcohol per week ¥¥defined as BMI >30kg/m² OR: odds ratio; aOR: adjusted odds ratio; QTc: QT interval corrected for heart rate using Bazett's formula (QT/RR^{1/2}); prolonged QTc defined as QTc >460ms for women and as QTc >450ms for men							