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Predictors of electrocardiographic QT interval prolongation in men with HIV

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Abstract

Objective—HIV-infected (HIV+) individuals may be at increased risk for sudden arrhythmic cardiac death. Some studies have reported an association between HIV infection and prolongation of the electrocardiographic QT interval, a measure of ventricular repolarisation, which could potentiate ventricular arrhythmias. We aimed to assess whether HIV+ men have longer QT intervals than HIV-uninfected (HIV−) men and to determine factors associated with QT duration.

Methods—We performed resting 12-lead ECGs in 774 HIV+ and 652 HIV− men in the Multicenter AIDS Cohort Study (MACS). We used multivariable linear and logistic regression analyses to assess associations between HIV serostatus and Framingham corrected QT interval (QTc), after accounting for potential confounders. We also determined associations among QTc interval and HIV-related factors in HIV+ men. In a subgroup of participants, levels of serum markers of inflammation were also assessed.

Results—After adjusting for demographics and risk factors, QTc was 4.0 ms longer in HIV+ than HIV− men ($p<0.001$). Use of antiretroviral therapy (ART), specific ART drug class use and other HIV-specific risk factors were not associated with longer QTc. Among the subgroup with inflammatory biomarker measurements, higher interleukin-6 (lL-6), intercellular adhesion molecule-1 (lCAM-1) and B-cell activating factor levels were independently associated with longer QTc and their inclusion partially attenuated the HIV effect.

Conclusions—HIV+ men had longer QTc, which was associated with higher levels of systemic inflammatory factors. This longer QTc may contribute to the increased risk for sudden arrhythmic cardiac death in some HIV+ individuals.

INTRODUCTION

Prolongation of the QT interval on surface ECGs reflects prolonged ventricular repolarisation and is associated with increased risk of cardiovascular and all-cause mortality in the general population.[1] QT interval prolongation may predispose individuals to sudden arrhythmic cardiac death (SCD) by increasing the propensity for sustained ventricular arrhythmias. Even mild increases in the QT interval, below clinical significance, may nonetheless increase susceptibility for QT-related arrhythmias in the presence of multiple insults that affect ventricular repolarisation, that is, the concept of repolarisation reserve.[2]

HIV-infected (HIV+) individuals may be at particularly increased risk for SCD. Recently, a 4.5-fold elevated risk for SCD was described among attendees at an HIV clinic compared with estimated rates in the general population.[3] Pathophysiological mechanisms for this increased risk are incompletely understood but may relate to greater susceptibility for QT interval prolongation. Potential multifactorial causes of prolonged QT interval in HIV-infected individuals include: (1) direct prolongation induced by some antiretroviral agents, including protease inhibitors (PIs)[4] and non-nucleoside reverse transcriptase inhibitors (NNRTIs)[5] (eg, efavirenz and rilpivirine, each of which is part of a fixed-dose combination regimen and can prolong the QT in a dose-dependent manner); (2) drug-drug interactions between antiretroviral therapy (ART) and cytochrome-P450-dependent QT-prolonging drugs[6]; (3) direct HIV virus effects on cardiac ion hERG K+ channels that modulate QT

intervals[78]; and (4) illicit drug use, particularly opioids,[9] which also block the HERG K+ channel.[10]

Results of prior studies evaluating the prevalence and causes of QT interval prolongation among HIV+ persons have been inconsistent, have lacked comparable HIV-uninfected (HIV −) individuals or were small in size.[11–16] We sought to compare the QT interval duration in a large contemporary cohort that includes both HIV+ and concurrently enrolled at-risk but HIV− men and assess relative contributions of risk factors.

METHODS

The study population consisted of 1612 active participants in the Multicenter AIDS Cohort Study (MACS). The MACS is an ongoing prospective longitudinal study of the natural and treated histories of HIV-1 infection in men who have sex with men conducted at four US sites (Baltimore/Washington DC, Chicago, Pittsburgh and Los Angeles). Four waves of enrolment have occurred in 1984–1985, 1987–1991, 2001–2003 and 2010–2017. Enrollees participate in semiannual research visits where they undergo standardised interviews, physical examinations and blood and urine specimen collection and storage. We excluded participants with a prior history of myocardial infarction, stroke or heart failure (n = 49).

Data were collected for demographic, HIV clinical parameters and cardiac risk factors, including age, race, measured blood pressure, fasting serum glucose, fasting lipid panel, body mass index (BMI), self-reported smoking status and use of prescribed medications and recreational drugs, including opioids (eg, heroin). Medications were categorised into categories of QT prolongation risk using the publicly available database CredibleMeds.org, accessed 14 December 2017 (n = 140 drugs, see online supplementary table 1).[17] Hepatitis C virus (HCV) status was assessed by antibody and RNA testing (chronic infection defined as antibody positive and RNA positive). In HIV+ men, measures of HIV disease activity included plasma HIV RNA concentrations (quantified down to 50 copies/mL using the Roche ultrasensitive assay), CD4+ T cell counts, nadir CD4+ T cell counts, medical record confirmation of prior AIDS-defining malignancy or opportunistic infection and measures of ART including duration of highly active ART (HAART) use and use of PIs, efavirenz and rilpivirine.

Standard resting 12-lead ECGs were performed between 1 October 2016 and 1 October 2017. ECGs were recorded digitally at 10 mm/mV calibration at a speed of 25 mm/s for 10 s using GEMSIT MAC 1600 ECG machines (Marquette Electronics, Milwaukee, Wisconson, USA) and transmitted for centralised reading to the ECG Reading Center at the Epidemiological Cardiology Research Center, Wake Forest School of Medicine (Winston-Salem, North Carolina, USA).

In subsets of participants who also participated in ancillary MACS studies (subclinical atherosclerosis study by CT[18] and inflammation and immune activation biomarker study[19]), blood was analysed for levels of seventeen biomarkers, including acute phase reactants (fibrinogen, D-dimer and C reactive protein), serum cytokines (interleukin-6 (IL-6); B-cell activation factor (BAFF); and receptor activator of nuclear factor-kappa B ligand) and

soluble (s) immune receptors (sCD14; sCD27; sCD163; soluble IL-2 receptor alpha (sIL-2Ra); soluble IL-6 receptor alpha (sIL-6Ra); soluble β-receptor glycoprotein 130 (sGP130); intercellular adhesion molecule 1 (ICAM-1); soluble tumour necrosis factor-receptor 1 and soluble tumour necrosis factor-receptor 2 (sTNF-R2)); and chemokines (monocyte chemoattractant protein-1 (MCP1/CCL2) and chemokine C-X-C motif ligand 13 (CXCL13)). BAFF, CXCL13, sCD14, sCD27, sGP130, sIL-2Ra, sIL-6Ra and sTNF-R2 were measured at a median of 0.4 years (IQR 0–0.5 years) from the 12-lead ECG. Levels of the other inflammatory biomarkers were assessed at a median of 5.6 years (IRQ 4.8–6.2) before the ECG. See online supplementary table 2 for details of the biomarker assays.

The Institutional Review Boards of all participating sites approved the study, and all participants signed informed consent.

Analysis of electrocardiographic QT intervals

All ECG analyses were performed blinded to HIV serostatus. All ECGs were first inspected visually for quality, and processing was then performed automatically with the GE Marquette 12-SL programme 2001 version (GE Marquette, Milwaukee, Wisconsin, USA). For each tracing, a single global measure of the QT interval was defined as the time duration between the earliest QRS onset to the latest T-wave offset (end). We corrected the QT interval (corrected QT interval (QTc)) for the heart rate (RR interval) using both the traditional log-linear (Bazett) and the linear (Framingham and Hodges) correction formulae according to published recommendations for the standardisation and interpretation of the ECG[20]:

Framingham QTc = QT + 0.154 (1–RR interval)

Hodges QTc=QT+0.00175 ([60/RR interval] –60)

Bazett QTc = QT/(RR interval)$^{1/2}$

Tracings were excluded (n = 137) from analysis in the presence of poor quality (n=32), non-sinus rhythm (eg, atrial fibrillation/ flutter: n = 15 or paced atrial rhythm: n=5) or major intraventricular conduction defects (complete left or right bundle branch blocks, Wolff-Parkinson-White syndrome, ventricular pacemaker or any QRS duration exceeding 120 ms; n=85). The final sample size was n=1426.

Statistical methods

Continuous data are reported as mean values ± SD or as median values with IQRs. The distributions of demographic, behavioural and clinical characteristics among HIV+ and HIV- men were compared using the χ^2 or Wilcoxon rank sum tests for categorical and continuous variables, respectively. Primary analyses were performed using the Framingham-defined QTc with secondary analyses using the Bazett and Hodges definitions of QTc. We used the Framingham formula as the primary outcome since it provides optimal heart rate correction and is more closely associated with clinical outcomes.[2021]

Continuous QTc values between HIV+ and HIV− men were compared using linear regression. Residuals from the linear regression models were plotted to evaluate distributional assumptions and absolute studentized residuals ≥2.5 were used to identify and test the influence of potential outliers. Logistic regression was used to compare those with QTc above the clinical threshold of 450 ms to define prolonged QT in men.[20] We analysed the following models: model 1: unadjusted; model 2: adjusted for age, race, MACS site, wave of MACS enrolment (before/after 2001); model 3: further adjusted for BMI, heavy alcohol use >13 drinks/week, cumulative pack-year of smoking, use of opioids, systolic blood pressure, serum fasting glucose level, receipt of medications to treat hypertension or diabetes, estimated glomerular filtration rate, left ventricular hypertrophy (LVH) by Cornell criteria on ECG and use of QT prolongation drugs (known and possible vs conditional and none as identified by CredibleMeds.org as of 14 December 2017; n = 140 drugs, see online supplementary table 1)[17]; model 4: performed in the HIV+ men to explore HIV factors, including PI use, plasma HIV RNA (viral load) level modelled as a binary variable (below vs above 50 copies/mL), history of AIDS, current and nadir CD4+ T cell counts and duration of HAART, each in a separate model including covariates from model 3; and model 5: included inflammatory biomarker levels, each in a separate model in addition to the covariates from model 3. For the exploratory biomarker analysis, multiple comparisons were controlled for using the Benjamin-Hochberg method.[22] Biomarker levels were assessed as tertiles. We used multiple imputation (five times) to fill in missing covariates (8%) in models 3 and 5.

Statistical significance was defined as a p value <0.05. All analyses were performed using SAS V9.4.

RESULTS

Baseline characteristics are shown in table 1. The HIV+ men were younger and more likely to be of non-Caucasian race compared with the HIV− men. HIV+ men had slightly lower BMI, systolic blood pressure and lipid levels and higher prevalence of renal dysfunction and use of QT prolonging drugs compared with HIV− men. The majority of the measured inflammatory biomarker levels were higher in the HIV+ compared with to HIV-− men. Most HIV+ men (83%) were virally suppressed and were on HAART for a median of 12.1 years. Average QTc did not differ between HIV+ and HIV- men by the Framingham (412±19 vs 411±20 ms, p = 0.47) and Hodges formulae (412±19 vs 413±20 ms, p = 0.92) in unadjusted analyses, but was slightly longer in HIV+ individuals by the Bazett formula (420±24 vs 417±24 ms, p = 0.018). The proportion of individuals with QTc above 450 ms was similar in the HIV+ and HIV− groups (3% for both by Framingham, p = 0.58).

Associations of HIV serostatus and cardiovascular risk factors with QTc duration (Framingham) as a continuous variable using multivariable linear regression are shown in table 2. In the fully adjusted model (model 3), there was a significant 4.0 ms (95% CI 1.8 to 6.1; p<0.001) longer QTc in HIV+ compared with HIV− men. Longer QTc was also significantly associated with older age, higher BMI, heavy alcohol use, higher systolic blood pressure, treatment for hypertension and LVH on ECG.

Among HIV+ men, HIV-related factors were not associated with continuous QTc duration (model 4, table 3) suggesting an unexplained contribution to the observed QTc lengthening in HIV+ men. We investigated possible explanations for this observation by performing an exploratory analysis of associations between inflammatory biomarker levels and QTc. There were dose-dependent associations between increasing tertiles of IL-6, ICAM-1 and BAFF levels and longer QTc duration after accounting for multiple comparisons when each biomarker was added individually to model 3 (table 4). Moreover, addition of the biomarkers attenuated the HIV association with QTc duration (table 4). Among individuals with all three available biomarker levels (n=574), HIV+ serostatus was associated with a 4.4 ms longer QTc, which declined to 4.0 ms after addition of IL-6 level tertiles. After accounting for ICAM-1 level tertiles, the QTc difference associated with HIV decreased to 3.4 ms and was no longer significant (95% CI −0.3 to 7; p = 0.08). Similarly, with addition of BAFF level tertiles, the QTc duration declined to 3.2 msec with non-significant p value (95% CI −0.4 to 6.9; p = 0.08) in the adjusted model. Similar trends were seen among the 531 men with suppressed viral load (<50 copies). There were no significant associations between QTc and the remaining 14 inflammatory biomarker levels after accounting for multiple comparisons.

We also explored whether HCV coinfection could partially explain the HIV association with QTc but found no relationship with QTc when HCV status was added to model 3 (QTc difference of 1.4; 95% CI −3.4 to 6.1; p = 0.58).

Similar results were found with continuous QTc duration measured by the Hodges and Bazett formulae (results not shown). Trends were also similar when QTc duration was modelled as a binary variable (above and below the clinical threshold of 450 ms; online supplementary tables 3 and 4) though the number of participants with QTc above 450 ms was small (n=41, 3% of the overall cohort).

DISCUSSION

We found an association between HIV infection and QTc prolongation in a contemporary, well-characterised cohort of HIV+ men compared with a similar, concurrently enrolled HIV − group. HIV infection was independently associated with longer QTc duration after adjustment for demographics and risk factors. The HIV effect on QTc was not explained by traditional HIV risk factors but appeared to be at least partially mediated by systemic biomarkers of inflammation.

Findings from previously published studies highlight the occurrence of QTc prolongation in HIV+ persons but show significant variability in the identification of risk factors and potential mechanisms. Studies of ART-naïve HIV+ individuals from developing countries suggest an increased prevalence of QT prolongation compared with HIV− controls and support a significant direct HIV effect.[12] Among persons on ART, prior studies suggest longer QT intervals in those taking older PIs and NNRTIs.[11] In a 2007 nested case-control study of 650 HIV+ individuals on ART, the prevalence of prolonged QTc above 440 ms was 9.8%, and risk factors for QT prolongation included use of nelfinavir, efavirenz, methadone or cotrimoxazole, or excessive alcohol intake.[23] In a 2011 analysis of the Strategies for

Management of Antiretroviral Therapy study comparing ritonavir-boosted PI, non-boosted PI and NNRTI regimens, the overall prevalence of QTc prolongation above 440 ms was 9.6%.[24] QTc did not vary by boosted PI regimen; QTc was 1.5 ms lower in boosted PI groups compared with the NNRTI group.[24] A recent cross-sectional comparison of 496 HIV + individuals in the HIV-HEART study with sex-matched and age-matched HIV-uninfected controls from population-based German Heinz Nixdorf Recall Study[13] showed a significantly longer QTc in HIV+ males (424 ±23 vs 411±15 ms). The 12.5 ms QTc difference between cohorts remained significant after adjustment for QTc prolonging medications. The prevalence of QTc above 440 ms was 22.8% in HIV-infected compared with 3.9% in HIV uninfected; smoking was the only significant risk factor. Those prior studies are limited by lack of comparable HIV− controls, cohorts predating the availability of HAART and smaller sample sizes.

Our results confirm an independent association between treated HIV infection and QTc interval in a contemporary cohort of HIV+ men who have sex with men compared with a concurrently enrolled HIV− cohort with similar risk factors. However, the effect we observed (4.0 ms in our adjusted analyses) was less pronounced than the previously reported 12.5 ms difference in the HIV-Heart Study with a lower prevalence of significant QTc prolongation above 450 ms in HIV+ men (3% vs. their report of 22.8%).[13] We found no significant associations between QTc and medication use (HIV and non-HIV). The low prevalence of the use of QT-prolonging drugs, efavirenz and rilpivirine, decreased the power to detect a difference. We did find independent associations between QTc duration and heavy alcohol use, elevated blood pressure and treatment for hypertension, and LVH by ECG. LVH generally resulting from hypertension is known to cause repolarisation abnormalities that can prolong the QT. Interestingly, concomitant LVH and QT prolongation above the clinical threshold has been associated with incrementally higher mortality in the general population.[25] A prior study in a general population also observed an association between heavy alcohol consumption and QTc prolongation above the clinical threshold.[26] Both associations warrant further study in HIV cohorts.

The exploratory analysis revealed a novel association between levels of inflammatory biomarkers and QTc that could partially explain the observed effect of HIV-infection. Although not well-described in HIV+ individuals, there is mounting evidence to suggest that systemic inflammation may modulate ventricular repolarisation and prolong the QTc interval.[2728] Data from patients with chronic autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel diseases[2728] and from the general population[29] support an association between systemic inflammation levels and lengthening of the QTc interval. Inflammatory cytokines may directly affect the myocardium by inducing changes in potassium and calcium ion channel expression and function.[28] Alternatively, heightened systemic inflammation may lead to autonomic nervous system dysfunction that can then result in QT prolongation.[27]

It is important to note that many of the prior studies investigating the association between HIV serostatus and QT prolongation[11131423] used the non-linear Bazett formula for QTc calculation, which is currently not recommended by the clinical guidelines for electrocardiography standardisation.[20] The Bazett formula still remains the most commonly

used formula in clinical practice, however. Here, we used one of the preferred linear-adjusted formulae, Framingham, as the primary outcome, because it most optimally provides heart rate correction and is most closely associated with clinical outcomes.[2021] Hence, differences in our results compared with prior studies could be due to differences in the QTc formula used and highlight the importance of using the preferred linearly adjusted parameters.

There are limitations to the present study. The MACS includes only men, and it is unknown if the results may differ among HIV+ women. However, since QTc intervals vary dramatically as a function of sex, interrogating the effects within a homogeneous sample can be advantageous. There remains the potential for residual confounding due to the observational nature of the study. Inflammatory biomarker levels were not measured concurrently with the ECG. However, previous publications from the MACS have demonstrated long-term stability of these inflammatory biomarker levels beyond 1 year after HAART initiation and HIV suppression.[19] However, the present study has significant strengths including the large sample size from a cohort treated in the contemporary era, detailed characterisation of potential confounding and contributing factors and an HIV− comparison group of otherwise similar men at risk for HIV infection.

In conclusion, HIV+ men had longer QTc, which may be partially mediated by higher levels of systemic inflammatory biomarkers. Although the prevalence of clinically prolonged QTc duration above 450 ms was low, longer QTc duration, even in the normal range, may predispose some HIV+ individuals to ventricular arrhythmias and SCD via reduced repolarisation reserve. Even among virally suppressed HIV+ individuals, those with greater systemic inflammation may be at risk for longer QT intervals that could be further potentiated by additional QT-pro- longing insults and may warrant increased vigilance and electrocardiographic monitoring. This study also emphasises the need to use linear-adjusted QTc formulae such as Framingham, which most effectively limits heart rate effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Zhang Y, Post WS, Blasco-Colmenares E, et al. Electrocardiographic QT interval and mortality: a meta-analysis. Epidemiology 2011;22:660–70. [PubMed: 21709561]
2. Roden DM, Abraham RL. Refining repolarization reserve. Heart Rhythm 2011;8:1756–7. [PubMed: 21708111]
3. Tseng ZH, Secemsky EA, Dowdy D, et al. Sudden cardiac death in patients with human immunodeficiency virus infection. J Am Coll Cardiol 2012;59:1891–6. [PubMed: 22595409]
4. Anson BD, Weaver JG, Ackerman MJ, et al. Blockade of HERG channels by HIV protease inhibitors. Lancet 2005;365:682–6. [PubMed: 15721475]
5. Abdelhady AM, Shugg T, Thong N, et al. Efavirenz inhibits the human ether-a-go-go related current (herg) and induces qt interval prolongation in cyp2b6*6*6 allele carriers. J Cardiovasc Electrophysiol 2016;27:4206–13.
6. Manga P, McCutcheon K, Tsabedze N, et al. HIV and Nonischemic Heart Disease. JAm Coll Cardiol 2017;69:83–91. [PubMed: 28057254]
7. Es-Salah-Lamoureux Z, Jouni M, Malak OA, et al. HIV-Tat induces a decrease in IKr and IKs via reduction in phosphatidylinositol-(4,5)-bisphosphate availability. J Mol Cell Cardiol 2016;99:1–13. [PubMed: 27590098]
8. Bai YL, Liu HB, Sun B, et al. HIV Tat protein inhibits hERG K+ channels: a potential mechanism of HiV infection induced LQTs. J Mol Cell Cardiol 2011;51:876–80. [PubMed: 21820442]
9. Wedam EF, Haigney MC. The impact of Opioids on Cardiac Electrophysiology. Curr Cardiol Rev 2016;12:27–36. [PubMed: 26818485]
10. Zünkler BJ, Wos-Maganga M. Comparison of the effects of methadone and heroin on human ether-à-go-go-related gene channels. Cardiovasc Toxicol 2010;10:161–5. [PubMed: 20467834]
11. Gili S, Mancone M, Ballocca F, et al. Prevalence and predictors of long corrected QT interval in HIV-positive patients: a multicenter study. J Cardiovasc Med 2017;18:539–44.
12. Mcintosh RC, Lobo JD, Hurwitz BE. Current assessment of heart rate variability and QTc interval length in HIV/AIDS. Curr Opin HIV AIDS 2017;12:528–33. [PubMed: 28984702]
13. Reinsch N, Arendt M, Geisel MH, et al. Prolongation of the QTc interval in HIV-infected individuals compared to the general population. Infection 2017;45:659–67. [PubMed: 28776165]
14. Reinsch N, Buhr C, Krings P, et al. Prevalence and risk factors of prolonged QTc interval in HIV-infected patients: results of the HIV-HEART study. HIV Clin Trials 2009;10:261–8. [PubMed: 19723613]
15. Charbit B, Rosier A, Bollens D, 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]
16. Soliman EZ, Prineas RJ, Roediger MP, et al. Prevalence and prognostic significance of ECG abnormalities in HIV-infected patients: results from the Strategies for Management of Antiretroviral Therapy study. J Electrocardiol 2011;44:779–85. [PubMed: 21145066]
17. Woosley RL, Heise CW, Romero KA, et al. QTdrugs List, AZCERT, Inc 1822 innovation Park Dr., Oro Valley, AZ 85755 www.CredibleMeds.org.
18. Ketlogetswe KS, McKibben R, Jacobson LP, et al. Osteoprotegerin, but Not Receptor Activator for Nuclear Factor-κB Ligand, is Associated With Subclinical Coronary Atherosclerosis in HIV-infected Men. JAcquir Immune Defic Syndr 2015;70:362–9. [PubMed: 26090754]
19. Ni Wada, Jacobson FP Margolick JB, et al. The effect of HAART-induced HIV suppression on circulating markers of inflammation and immune activation. AIDS 2015;29:463–71. [PubMed: 25630041]
20. Rautaharju PM, Surawicz B, Gettes FS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American heart association electrocardiography and arrhythmias committee, council on clinical cardiology; the american

college of cardiology foundation; and the heart rhythm society: Endorsed by the international society for computerized electrocardiology. Circulation 2009;119:e241–e250. [PubMed: 19228821]

21. Vandenberk B, Vandael E, Robyns T, et al. Which QT Correction Formulae to Use for QT Monitoring? J Am Heart Assoc 2016;5.
22. Hochberg Y, Benjamini Y More powerful procedures for multiple significance testing. Stat Med 1990;9:811–8. [PubMed: 2218183]
23. Chinello P, Fisena FP, Angeletti C, et al. Role of antiretroviral treatment in prolonging QTc interval in HIV-positive patients. J Infect 2007;54:597–602. [PubMed: 17174400]
24. Soliman EZ, Fundgren JD, Roediger MP, et al. Boosted protease inhibitors and the electrocardiographic measures of QT and PR durations. AIDS 2011;25:367–77. [PubMed: 21150558]
25. Soliman EZ, Shah AJ, Boerkircher A, et al. inter-relationship between electrocardiographic left ventricular hypertrophy and QT prolongation as predictors of increased risk of mortality in the general population. Circ Arrhythm Electrophysiol 2014;7:400–6. [PubMed: 24762807]
26. Fi Z, Guo X, Fiu Y, et al. Relation of heavy alcohol consumption to QTc interval prolongation. Am J Cardiol 2016;118:1201–6. [PubMed: 27561189]
27. Fazzerini PE, Capecchi PF, Faghi-Pasini F. Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis. Eur Heart J 2017;38:1717–27. [PubMed: 27252448]
28. Fazzerini PE, Faghi-Pasini F, Bertolozzi I, et al. Systemic inflammation as a novel QT-prolonging risk factor in patients with torsades de pointes. Heart 2017;103:1821–9. [PubMed: 28490617]
29. Fazzerini PE, Capecchi PF, Faghi-Pasini F. Fong QT Syndrome: An emerging role for inflammation and immunity. Front Cardiovasc Med 2015;2:26. [PubMed: 26798623]

Key message

What is already known on this subject?

- There is a reported increased risk for sudden cardiac death in HIV+ individuals, but the aetiologies and mechanisms are unclear.

What might this study add?

- Prior studies of QT prolongation among HIV+ persons have been equivocal due to limitations in sample size, lack of comparable HIV- comparison groups and heterogeneity in corrected QT interval (QTc) quantification methodology. In a large, well-characterised, concurrently enrolled cohort of HIV+ and HIV − men, we found an association between HIV serostatus and QT prolongation that may be at least partially explained by higher levels of systemic inflammation, rather than HIV-specific risk factors such as drug class use, including protease-inhibitor use, plasma HIV viraemia and CD4 T cell counts. Moreover, it emphasises the need to use linear- adjusted QTc formulae such as Framingham rather than the widely used Bazett formula.

How might this impact on clinical practice?

- Our results highlight another potential adverse cardiovascular consequence of heightened systemic inflammation in

HIV+ individuals and emphasise the need for caution and vigilance when prescribing one or more QT-prolonging drugs. Optimal calculation of QTc using linear-adjusted formulae is also emphasised.

Table 1

Characteristics of the study cohort by HIV serostatus

	N (%)		
	HIV uninfected (n=652)	**HIV- infected (n=774)**	**P values**
Age in years; median (IQR)	61.0 (54.4–67.2)	54.4 (46.9–60.6)	<0.001
Race (%)			
Caucasian	471 (72)	370 (48)	<0.001
Black	118 (18)	255 (33)	
Hispanic/other	63 (10)	149 (19)	
MACS site			
Baltimore	154 (24)	187 (24)	0.012
Chicago	104 (16)	172 (22)	
Pittsburgh	191 (29)	188 (24)	
Los Angeles	203 (31)	227 (29)	
Enrolled after 2001	232 (36)	500 (65)	<0.001
Education level (below 12 years)	91 (14)	197 (25)	<0.001
Alcohol use >13 drinks per week	55 (7)	63 (10)	0.08
Cumulative pack-year of smoking	0.2 (0–17.4)	2 (0–19.5)	0.15
Body mass index (kg/m^2); median (IQR)	26.6 (23.8–30)	25.9 (23.2–29.1)	0.005
Systolic blood pressure (mm Hg); median (IQR)	130.5 (120–141)	128 (119–138)	0.001
On hypertension medications	242 (38)	255 (33)	0.09
On diabetes medications	59 (9)	72 (9)	0.89
On cholesterol lowering medications	225 (35)	265 (35)	0.87
Opioid use	42 (6)	61(8)	0.30
HCV infection	24 (4)	50 (7)	0.011
Fasting glucose (mg/dL); median (IQR)	94 (87–103)	94 (87–103)	0.69
Total cholesterol (mL/dL); median (IQR)	179 (157–203)	176 (149–200)	0.025
HDL cholesterol (mL/dL); median (IQR)	50.4 (42.9–60)	46 (40–56)	<0.001
eGFR below 60 mL/min/m^2	46 (7)	85 (11)	0.011
QT prolongation drugs (known+possible)	46 (7)	93 (12)	0.002
Biomarkers; median (IQR)			
BAFF (ng/mL, n=580 HIV−/637 HIV+)	2.4 (2.1–2.9)	2.7 (2.2–3.2)	<0.001
CXCL13 (ng/mL, n=580 HIV−/637 HIV+)	0.4 (0.3–0.5)	0.5 (0.3–0.6)	<0.001
sCD14 (ng/mL, n=580 HIV−/637 HIV+)	1818 (1540–2160)	1950 (1634–2297)	<0.001
sCD27 (ng/mL, n=580 HIV−/637 HIV+)	11.2 (9.2–14)	13.5 (10.6–16.9)	<0.001
sGP130 (ng/mL, n=580 HIV−/637 HIV+)	165 (151–183)	170 (151–188)	0.015
sIL-2Ra (ng/mL, n=580 HIV−/637 HIV+)	2.0 (1.5–2.5)	2.1 (1.7–2.7)	0.045
sIL-6Ra (ng/mL, n=580 HIV−/637 HIV+)	35.5 (28.5–44)	35.1 (28.8–43.9)	0.91
sTNF-R2 (ng/mL, n=580 HIV−/637 HIV+)	2.5 (2.1–2.9)	2.6 (2.2–3.3)	<0.001
CCL2 (MCP1) (pg/mL, n=256 HIV−/388 HIV+)	238 (184–305)	273 (210–346)	<0.001
CRP (ug/mL, n=255 HIV−/388 HIV+)	0.9 (0.5–1.8)	1.2 (0.6–2.8)	0.006
D-dimer (pg/mL, n=254 HIV−/385 HIV+)	0.2 (0.1–0.3)	0.2 (0.1–0.3)	0.009

	N (%)		
	HIV uninfected (n=652)	**HIV- infected (n=774)**	**P values**
Fibrinogen (mL/dL, n=255 HIV−/384 HIV+)	333 (293–372)	320 (275–365)	0.024
ICAM-1 (ng/mL, n=255 HIV−/388 HIV+)	225 (192–265)	259 (209–314)	<0.001
IL-6 (pg/mL, n=250 HIV−/385 HIV+)	1.2 (0.8–2.0)	1.5 (1.0–2.3)	0.004
RANKL (pg/mL, n=255 HIV−/386 HIV+)	13.8 (7.5–30.3)	7.8 (3.4–19.5)	<0.001
sCD163 (ng/mL, n=247 HIV−/376 HIV+)	538 (427–683)	657 (501–853)	<0.001
sTNF-R1 (pg/mL, n=256 HIV−/387 HIV+)	1141 (949–1321)	1175 (956–1467)	0.028
HIV factors			
HIV RNA (viral load), <50 copies/mL		636 (83)	
HIV RNA copy number per mL if detectable; median (IQR)		318 (86–6639)	
CD4+ T cell count (cells/mm^3); median (IQR)		698 (521–884)	
Nadir CD4+ T cell count (cells/ mm^3); median (IQR)		335 (216–467)	
On HAART		698 (91)	
Duration of HAART (years); median (IQR)		12.1 (4.4–16.4)	
On protease inhibitor (PI)		183 (24)	
Duration of PI use (years); median (IQR)		3.7 (0–11.4)	
On efavirenz		21 (3)	
On rilpivirine		8 (1)	
History of AIDS		74 (10)	
ECG parameters			
Heart rate (bpm); median (IQR)	64 (56–72)	67 (59–74)	<0.001
QRS duration (ms); median (IQR)	90 (83.5–96)	88 (84–96)	0.23
LVH by Cornell voltage	7 (1)	12 (2)	0.43
QTc duration (Framingham) (ms) (SD)	411.3 (20)	412.1 (19.2)	0.47
Clinical threshold >450 (%)	17 (3)	24 (3)	0.58
QTc duration (Bazett) (ms) (SD)	416.7 (23.9)	419.8 (23.9)	0.018
Clinical threshold >450 (%)	57 (9)	84 (11)	0.18
QTc duration (Hodges) (ms) (SD)	412.6 (19.9)	412.4 (19.4)	0.92
Clinical threshold >450 (%)	20 (3)	19 (2)	0.48

BAFF, B-cell activating factor; CRP, C reactive protein; CXCL13, chemokine C-X-C motif ligand 13; eGFR, estimated glomerular filtration rate; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HDL, high-density lipoprotein; ICAM-1, intercellular adhesion molecule 1; IL-6, interleukin-6; LVH, left ventricular hypertrophy; MACS, Multicenter AIDS Cohort Study; QTc, corrected QT interval; RANKL, receptor activator of nuclear factor-kappa B ligand; sGP130, soluble β-receptor glycoprotein 130; sIL-2Ra, soluble IL-2 receptor alpha; sIL-6Ra, soluble IL-6 receptor alpha; sTNFR1, soluble tumour necrosis factor-receptor 1; sTNFR2, soluble tumour necrosis factor-receptor 2; ECG (electrocardiography); CCL2, chemokine (C-C motif) ligand 2; soluble CD163 (sCD163); soluble CD14 (sCD14); soluble CD27 (sCD27).

Table 2

Risk factors for longer continuous QTc duration (Framingham) among all 1426 participants* in univariate (model 1), partially adjusted (model 2) and fully adjusted (model 3) analyses

	Model 1		Model 2		Model 3	
	Mean difference (95% CI)	**P values**	**Mean difference (95% CI)**	**P values**	**Mean difference (95% CI)**	**P values**
HIV Infected (vs uninfected)	0.7 (−1.3 to 2.8)	0.48	3.4 (1.3 to 5.5)	0.001	4.0 (1.8 to 6.1)	<0.001
Age per 5 years			2.4 (1.9 to 2.9)	<0.001	2.2 (1.5 to 2.8)	<0.001
Race						
Black (vs Caucasian)			−0.5 (− 3.2to 2.1)	0.70	−1.2 (− 3.8 to 1.5)	0.39
Hispanic/other (vs Caucasian)			0.3 (− 3.0 to 3.6)	0.86	0.5 (−2.8 to 3.8)	0.76
Enrolled after 2001			1.6 (−1.2 to 4.4)	0.25	1.1 (−1.7 to3.8)	0.46
Body mass index (kg/m^2)					2.0 (1.0 to 3.1)	<0.001
Alcohol use >13 drinks per week					5.0 (1.5 to 8.5)	0.005
Cumulative pack-year of smoking					0.0 (−0.1 to 0.0)	0.63
Opioid use					2.3 (−1.4 to 6.1)	0.22
Systolic blood pressure (mm Hg)					1.1 (0.5 to 1.8)	0.001
Fasting glucose (mg/dL)					−0.2 (−0.6 to 0.2)	0.26
On hypertension medications					2.6 (0.3 to 4.8)	0.027
On diabetes medications					−1.5 (−5.5 to 2.5)	0.47
eGFR per mL/min/1.73 m^2					0.0 (−0.1 to 0.1)	1.00
LVH on ECG (Cornell voltage)					16.6 (8.1 to 25)	<0.001
QT prolongation drugs (known+possible vs conditional+none)					2.5 (−0.8 to 5.8)	0.13

* Models 2 and 3 further controlled for MACS enrolment site.

MACS, Multicenter AIDS Cohort Study; QTc, corrected QT interval.

Table 3

HIV-specific risk factors for longer continuous QTc duration (Framingham) among the 774 HIV+ participants *

	Mean QT difference (ms, 95% CI)	P values
Duration of HAART (years)	0.2 (−0.1 to 0.5)	0.12
Nadir CD4+ T cell count <500 cells/mm^3	−2.2 (−5.4 to 1.1)	0.19
Current CD4+ T cell count <500 cells/mm^3	−1.0 (−4.2 to 2.1)	0.52
Undetectable HIV RNA viral load (<50 copies/mL)	−2.5 (−6.1 to 1.0)	0.16
History of AIDS	−01.7 (−6.3 to 2.9)	0.48
On protease inhibitors (PI)	0.9 (−2.2 to 4.0)	0.56
Cumulative years of PI use	0 (−0.2 to 0.2)	0.90
On efavirenz	1.0 (−7.0 to 9.1)	0.80
Cumulative years of efavirenz use	−0.1 (−0.3 to 0.2)	0.67
On rilpivirine	11.0 (−2.0 to 24)	0.10
Cumulative years of rilpivirine use	−0.7 (−2.0 to 0.5)	0.26

* Each HIV factor was assessed In a separate model with adjustment for age, race, MACS site, wave of MACS enrolment (before/after 2001), body mass Index, heavy alcohol use, cumulative pack-year of smoking, use of opioids, systolic blood pressure, serum fasting glucose level, eGFR, receipt of medications to treat hypertension or diabetes, left ventricular hypertrophy and use of QT prolongation drugs (known and possible vs condition and none).

eGFR, estimated glomerular filtration rate; HAART, highly active antiretroviral therapy; MACS, Multicenter AIDS Cohort Study; QTc, corrected QT interval.

Table 4

Adjusted associations between HIV infection, inflammatory biomarker levels and longer continuous QTc duration (Framingham) among the 574 men (230 HIV− and 344 HIV+) with all three available inflammatory biomarker testing results

	Adjusted model*		Adjusted model + IL-6		Adjusted model+ICAM-1		Adjusted model+BAFF	
	Mean QT difference (ms, 95% CI)	P value	Mean QT difference (ms, 95% CI)	P value	Mean QT difference (ms, 95% CI)	P value	Mean QT difference (ms, 95% CI)	P values
HIV infection (vs uninfected)	4.4 (0.8 to 8.1)	0.02	4.0 (0.4 to 7.6)	0.03	3.4 (−0.3 to 7.1)	0.07	3.2 (−0.4 to 6.9)	0.08
IL-6, Ist tertile (ref)			-	-				
IL-6, 2nd tertile (vs ref)			4.9 (0.9 to 8.8)	0.02				
IL-6, 3rd tertile (vs ref)			5.2 (1.2 to 9.2)	0.01				
ICAM-1, Ist tertile (ref)					-	-		
ICAM-1, 2nd tertile (vs ref)					3.7 (−0.2 to 7.6)	0.07		
ICAM-1,3rd tertile (vs ref)					5.6 (1.4 to 9.9)	0.01		
BAFF, Ist tertile (ref)							-	-
BAFF, 2nd tertile (vs ref)							−0.8 (−4.8 to 3.1)	0.68
BAFF, 3rd tertile (vs ref)							5.4 (1.2 to 9.6)	0.01

These three biomarkers remained significant after accounting for multiple comparisons using the Benjamin-Hochberg method. Results for the other biomarkers were not significant and are not shown here.

*The adjusted model controls for age, race, MACS site, wave of MACS enrolment (before/after 2001), HIV, body mass index, heavy alcohol use, cumulative pack-year of smoking, use of opioids, systolic blood pressure, serum fasting glucose level, eGFR, receipt of medications to treat hypertension or diabetes, left ventricular hypertrophy, and use of QT prolongation drugs (known and possible vs condition and none).

eGFR, estimated glomerular filtration rate; ICAM-1, intercellular adhesion molecule-1; MACS, Multicenter AIDS Cohort Study; QTc, corrected QT interval.