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Prolonged QTc in HIV-Infected Patients: A Need for Routine ECG Screening

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Abstract

Background: With HIV-infected patients living longer, there is an increased burden of comorbidities related to aging, HIV itself, and polypharmacy. Cardiac morbidity is of particular importance. **Methods:** This 2-group comparison study (156 HIV-positive and 105 HIV-negative patients) investigated the prevalence of abnormalities in and factors associated with an electrocardiogram (ECG) measure, corrected QT interval (QTc), where prolongation can lead to arrhythmia and sudden death. Medications prescribed (antiretroviral therapy, psychiatric medications, methadone, and antibiotics) at the time of ECG were noted. Patient characteristics, medications, QTc, and ECG characteristics were compared between the 2 groups. **Results:** Prolongation (29% versus 19%) and extreme prolongation (6% versus 1%) in QTc were more frequent in those with HIV. Antiretroviral therapy was associated with lower odds of prolonged QTc (odds ratio [OR] = 0.35; $P = .04$), while methadone with higher odds (OR = 4.6; $P = .01$) in HIV-positive patients. With methadone and medication groups adjusted, HIV status was still associated with 17-millisecond longer QTc ($P = .04$). **Conclusion:** This study provides evidence that patients with HIV may have clinically relevant longer QTc interval on ECG. Baseline and routine ECG monitoring may be warranted among patients living with HIV in clinical practice based on cumulative evidence.

Keywords

antiretroviral therapy, ECG, HIV, methadone, QT prolongation, QTc

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Introduction

Antiretroviral therapy (ART) allows patients infected with HIV to have an increased life span. With this comes increased prevalence of comorbidities, including cardiac disease and cardiac death as well as risk factors for cardiovascular disease (CVD).[1,2] One such factor is acquired abnormalities of the conduction system of the heart, in particular prolongation of the duration of ventricular systole, the electrical reflection on the resting electrocardiogram (ECG) noted as the QT interval as measured corrected for heart rate, known as corrected QT interval (QTc). Prolongation of this interval may lead to ventricular arrhythmias and death.[3]

Drug-induced long QTc can lead to Torsades de pointes (TdP), a form of ventricular tachycardia. This may be transient or deteriorate into ventricular fibrillation which generally results in cardiac arrest and sudden death. There is particularly higher risk for TdP when the QTc is >500 milliseconds or when a drug increases the baseline QTc by >60 to70 milliseconds.[3]

Studies have provided information on ECG abnormalities in patients infected with HIV[4-8] and have shown that HIV status is

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What Do We Already Know about This Topic?

As cardiovascular disease (CVD) is becoming one of the leading causes of morbidity and mortality in patients living with HIV, there is increasing information about the diagnosis and management of CVD in this patient population; however, relatively less information exists regarding electrocardiographic (ECG) abnormalities, in particular prolongation of the ECG QT segment in patients living with HIV.

How Does Your Research Contribute to the Field?

Our study represents a "real-life" (an urban HIV clinic) investigation of QT segment in patients infected with HIV and the potential effect of medications on the ECG.

What Are Your Research's Implications toward Theory, Practice, or Policy?

The 12-lead ECG is not routinely performed in patients infected with HIV, despite patients often being on medications that are known to prolong the QT segment (such as psychiatric medications, antibiotics, methadone); however, our research suggests that baseline and routine monitoring of the 12-lead ECG be incorporated into the care of these patients.

associated with longer QT interval.[9,10] The influence of ART and possibly the virus itself on the ECG and QT interval has been demonstrated[6,8]; however, there is less information on the influence of other medications and methadone, all of which can prolong the QT interval. Patients living with HIV are found to have a high prevalence of being on one or more of these medications,[11] thereby making knowledge of side effects, such as ECG abnormalities, an increasingly important part of their care. Monitoring with a 12-lead ECG, while on any medication that can prolong the QTc interval, is recommended in package inserts, but it is unclear how often this recommendation is being followed both in the general population and in HIV clinical practice and how often the QTc is increased to lengths defined as prolonged.

In addition, much of the current information on ECG abnormalities in patients infected with HIV comes from large randomized trials and cohort studies,[7,8] whereas our study reflects "real-life" care of patients in a dedicated HIV clinic. The primary objective of this study was to examine the prevalence and extent of QTc prolongation in patients infected with HIV accounting for use of medications that can prolong the QTc interval, compared to a group of reasonably comparable patients who were HIV negative but receiving primary care in the same HIV clinic. Secondary objectives were to investigate whether the 4 medication groups of interest (ART, psychiatric medication, methadone, and antibiotics) are associated with QTc prolongation. We hypothesized that the prevalence of prolonged QTc is higher in HIV-infected patients compared to those who were HIV negative. Another (qualitative) objective was to help decide whether routine monitoring of the 12-lead ECG is justified in patients living with HIV based on our data as a part of the body of the related literature.

Methods

Study Design, Participant, and Setting

We conducted a cross-sectional, 2-group comparison study (with HIV-positive and HIV-negative patients) with retrospective chart review at the St Luke and Roosevelt Hospitals' HIV clinic in New York City, a designated New York State AIDS Center. The clinic provides care for both HIV-positive and HIV-negative patients. The HIV-negative patients included family and partners of HIV-positive patients and patients at risk of HIV. Patients from the 2 groups (HIV positive and HIV negative) were not matched.

Study participants were included if they were patients in the HIV clinic in the calendar year 2012 and had a 12-lead ECG in 2012, and we could verify their clinical status (ie, no acute cardiac or other event) and what medications they were on at the time of the ECG. HIV-positive and HIV-negative patients were selected from an alphabetized list. Of note, ECGs were performed for a number of reasons including as part of a preoperative evaluation, chest pain, and routine health care. Exclusions were age <18 years old or pregnancy. As illicit drug use and electrolyte disturbances can prolong QTc,[12] we excluded participants whose ECG appeared to have been performed at the time of acute illicit drug intoxication, acute electrolyte disturbances, or acute cardiac status such as myocardial infarction or congestive heart failure, for example, those who were clinically unstable in an ambulatory setting.

Medications

A search for medications linked to the time of an ECG was conducted using the electronic medical records (EMRs). Medications abstracted focused on ART, methadone, psychiatric medications, and antibiotics, which have been reported to prolong the QT.[7,13-15] Use of these medications was confirmed by verifying that the medications were on the medication list in the EMR at the time the ECG was performed and was on the list of medications in the clinical note (outpatient, inpatient, emergency department note, etc) associated with the time the ECG was performed. The list of psychiatric medications and antibiotics is provided in Supplementary Table S1.

ECG Interpretations

The ECGs were interpreted by a board-certified cardiologist (M.M.). As the clinical significance of the QT duration is influenced by heart rate, the QT interval corrected to heart rate (QTc) was calculated. Both the Bazett[16] and the Fridericia[17] formulas were used in the analyses, where the Bazett formula may overcorrect at higher heart rates. Prolonged QTc was

defined as ≥450 milliseconds for men and ≥460 milliseconds for women, and extremely prolonged QTc was defined as ≥500 milliseconds based on both formula (using "or" in the derived variable). Short QTc was defined as <340 milliseconds.[18,19] Cutoffs were based on those used in the literature for HIV-positive patients and patients on methadone and certain psychiatric medications.[7,20]

Other ECG measures (rate, sinus rhythm, atrial fibrillation/flutter, other non-sinus rhythm, and PR interval) were measured by the computer program, MAC 55 (General Electric, Boston, Massachusetts) and verified by the reading cardiologist (M.M.). Abnormalities (left bundle branch block, right bundle branch block, Q waves, and left ventricular hypertrophy) were classified according to the Minnesota ECG Code Classification system.[21]

Data Analysis

Standard descriptive statistics were used to summarize data, such as mean, standard deviation, interquartile range, and percentage. We used *t* test and Fisher exact test to compare continuous and categorical variables, respectively, between HIV-positive and HIV-negative patient groups.

Simple logistic regression was fit to estimate the unadjusted odds ratio (OR) between each of the patient factors and the prolonged QTc [as binary outcome, prolongation either by the Bazett or Fridericia formula] along with the 95% confidence intervals (CIs); models were fit separately for HIV-positive and for HIV-negative patients, as some factors are relevant to HIV-positive patients only. After that, multiple logistic regression was fit to estimate the adjusted ORs in HIV-positive and HIV-negative patients combined (for larger sample size and stable estimation); we fitted a full model (with all covariates included) as well as a parsimonious model after backward elimination was used to select statistically significant associations. In these regressions, we considered the list of covariates that were selected a priori, which were gender, race/ethnicity, methadone, psychiatric medications, antibiotics, ART, viral load, and CD4 count.

In addition, we fitted a multiple linear regression for QTc (as a continuous outcome) with the 4 medication groups with a particular interest in determining whether HIV status is associated with longer QTc even after adjusting for the use of methadone, which is well known to prolong QTc. As a sensitivity analysis, we repeated (1) the regression model fits with the addition of diabetes as a covariate, which was seen in unbalanced proportions in the 2 comparison groups; (2) after excluding patients on methadone; and (3) multiple logistic regression fits in full sample and subgroups of HIV-positive or HIV-negative patients, where (2) and (3) are recommended by reviewers and results are presented in the Supplement. SAS version 9.4 (SAS Institute) was used for data analysis.

Ethical Approval and Informed Consent

Institutional review board at St Luke's–Roosevelt Hospital Center determined that the protocol meets the ethical approval qualifications and was "exempt" for requirements of informed consent (IRB#: 11-008X).

Results

Demographic and Clinical Characteristics

A total of 261 participants were included in the analysis, of who 156 were HIV positive and 105 were HIV negative. There were no significant differences in demographic variables between persons with HIV and without HIV infection. The majority were male in both groups (76% and 81%, respectively; see Table 1). The CVD risk factor distribution was similar between the 2 groups, with the exception of diabetes; 11% of persons with HIV were diabetic compared to 27% of those without HIV infection ($P < .001$). Additionally, 36% of patients with HIV reported current smoking when compared to 25% of those without HIV, and 37% of persons with HIV were prescribed a statin when compared to 27% of those without HIV (both $P = .08$).

Medications

The majority of participants with HIV were on ART (88%). The ART regimens included nucleoside (tide) reverse transcriptase inhibitors in 83% of participants, protease inhibitors in 47% of participants, nonnucleoside reverse transcriptase inhibitors (NNRTIs) in 33% of participants, and integrase inhibitors in 20% of participants. The mean CD4 count was 562 cells/mm^3, and 69% had undetectable viral load at last laboratory check.

Methadone use was more common among participants with HIV (8.3%), compared to HIV-uninfected participants (2.9%; $P = .11$), and overall use of antibiotics that are known to prolong QTc was notably different in the 2 groups (19% versus 1%; $P < .0001$). There were no differences in psychiatric medication use between the 2 groups (37% versus 32%; $P = .61$; see Table 2).

Electrocardiogram Results

There was a difference in the mean QTc length as well as the proportion of patients having QTc prolongation—mean of 404 versus 391 milliseconds HIV-positive versus HIV-negative patients ($P = .009$), 29% versus 19% ($P = .08$) for prevalence of prolongation, and 6% versus 1% ($P = .05$) for extreme prolongation, respectively. Clinical information on those with marked QTc prolongation (≥500 milliseconds) is shown in Supplementary Table S2. Overall, they were more male on ART with undetectable viral load. Not all were on methadone and/or psychiatric medications. Detailed review of 12-lead ECG for additional abnormalities did not demonstrate

Table 1. Demographics and Characteristics.[a]

Demographic and Clinical Characteristics	HIV Positive, n = 156	HIV Negative, n = 105	*P* Value
Age, years, mean (SD)	52.4 (10.4)	52.2 (11.7)	.85
Male, n, %	119, 76%	85, 81%	.45
Race, n, %, African American	80, 52%	48, 46%	.58
Hispanic	52, 34%	36, 34%	
White	21, 14%	20, 19%	
Smoking, n, %			.08
Current	54, 36%	26, 25%	
Past	19, 13%	22, 21%	
Alcohol, n, %			.47
Current	4, 3%	5, 5%	
Past	20, 13%	10, 10%	
Illicit drug use, n, %			.23
Current	24, 16%	11, 11%	
Past	52, 34%	30, 29%	
Body mass index, in kg/m^2, mean (SD)	28.4 (6.4)	30.1 (6.2)	.10
Dyslipidemia, n, %	67, 43%	39, 37%	.37
Hypertension, n, %	83, 53%	59, 56%	.70
Diabetes, n, %	17, 11%	28, 27%	.001
Statins, n, %	58, 37%	28, 27%	.08
Coronary artery disease, n, %	23, 15%	11, 10%	.35
Coronary artery disease equivalent, n, %	4, 2.6%	2, 1.9%	1.0
Hepatitis C, n, %			.45
C	11, 7.1%	11, 10%	
B	1, 0.6%	0, 0%	
HIV-Related Characteristics			
Mode transmission n, %			
Men who have sex with men	71, 47%		
Heterosexual	47, 31%		
Intravenous drug addicts	27, 18%		
Others	5, 4%		
On antiretroviral therapy (ART), n, %	138, 88%		
Years on ART, in years, mean (SD)	8.3 (5.4)	NA	
CD4 count, cells/mm^3, mean (SD)	562 (337)		
Viral load, copies/mL			
Among detected, median (interquartile range)	534 (146-6861)		
Undetected, n, %	108, 69%		
Missing, n, %	4, 3%		

Abbreviations: SD, standard deviation; NA, not applicable.
[a]Percentage is within each subgroup (stratified by HIV status) excluding missing data. For continuous variables, we used *t* test, and for categorical variables, we used Fisher exact test.

statistically significant differences between the 2 groups (see Tables 3 and 4).

Factors Associated with QTc Prolongation

Univariate association was examined between various characteristics that have been suspected to be linked to QTc prolongation in HIV-positive and HIV-negative patients separately;

Table 2. Medications.[a]

Medication, n, %	HIV Positive, n = 156	HIV Negative, n = 105	*P* Value
Antiretroviral	138, 88%		
Nucleoside (tide) reverse transcriptase inhibitors	129, 83%		
Nonnucleoside reverse transcriptase inhibitors	52, 33%	NA	NA
Integrase inhibitor	31, 20%		
C-C chemokine receptor type 5	3, 2%		
Fusion inhibitor	1, 0.6%		
Protease inhibitor	74, 47%		
Methadone	13, 8.3%	3, 2.9%	.11
Psychiatric medication	58, 37%	34, 32%	.51
Antibiotics	30, 19%	1, 1%	<.0001

Abbreviation: NA, not applicable.
[a]Percentage is within each subgroup (stratified by HIV status) excluding missing data. See Supplementary Table S1 for details on psychiatric medications and antibiotics.

Table 3. Electrocardiogram Characteristics.[a]

Electrocardiogram Characteristics	HIV Positive, n = 156	HIV Negative, n = 105	*P* Value
Normal sinus rhythm, n, %	115, 73.7%	76, 72.4%	.89
Rate, beats/minute, mean (SD)	72.2 (15.3)	73.3 (15.8)	.56
PR msec, mean (SD)	215 (172)	183 (126)	.08
Left bundle branch block, n, %	2, 1.3%	2, 1.9%	1.0
Right bundle branch block, n, %	4, 2.6%	4, 3.8%	.72
Q wave, n, %	2, 1.3%	0, 0%	.52
Left ventricular hypertrophy, n, %	21, 13.6%	7, 6.7%	.10
Atrial fibrillation/flutter, n, %	1, 0.6%	2, 1.9%	.57

Abbreviation: SD, standard deviation.
[a]Percentage is within each subgroup (stratified by HIV status) excluding missing data. For continuous variables, we use *t* test, and for categorical variables, we use Fisher exact test.

Table 4. QTc Characteristics.[a]

QTc Characteristics	HIV Positive, n = 156	HIV Negative, n = 105	*P* Value
QT, milliseconds, mean (SD)	403.8 (42.1)	390.7 (34.6)	.007
QTc Bazett, milliseconds, mean (SD)	435.2 (35.2)	423.2 (29.4)	.005
QTc Fridericia, milliseconds, mean (SD)	425.1 (29.9)	413.6 (24.4)	.0007
Prolonged QTc, n, %	45, 28.9%	20, 19.1%	.08
Extremely prolonged QTc, n, %	10, 6.4%	1, 1.0%	.05
Short QTc, n, %	0%	0%	NA

Abbreviations: NA, not applicable; SD, standard deviation.
[a]Percentage is within each subgroup (stratified by HIV status) excluding missing data. For continuous variables, we use *t* test, and for categorical variables, we use Fisher exact test.

Table 5. Univariate Association of Characteristics and Medications with Prolonged QTc.[a]

	HIV Positive, n = 156		HIV Negative, n = 105	
Characteristics	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Male	1.13 (0.49-2.57)	.78	0.93 (0.27-3.15)	.90
African American versus white	1.17 (0.43-3.20)	.76	1.58 (0.39-6.45)	.52
Hispanic versus white	0.45 (0.14-1.42)	.17	1.45 (0.33-6.33)	.62
Methadone	4.58 (1.41-14.9)	.01	2.18 (0.19-25.4)	.53
Psychiatric medication	1.04 (0.51-2.12)	.92	1.51 (0.55-4.14)	.42
Antibiotics	1.30 (0.55-3.05)	.55	Model fit questionable	
Antiretroviral therapy	0.35 (0.13-0.96)	.04	NA	
Viral load				
Detectable versus not	0.93 (0.43-2.04)	.86		
Missing versus not	2.48 (0.34-18.4)	.37		
CD4 count <200 cells/mm^3	2.20 (0.80-6.01)	.13		

Abbreviations: CI, confidence interval; NA, not applicable; QTc, corrected QT interval.
[a]Odds ratio is unadjusted for other factors in simple logistic regression with QTc prolongation as binary outcome. Due to small sample size, Asian (N = 1) is combined with white and missing race (N = 2) is combined with African American (as the most common race). *P* values are unadjusted for multiplicity.

Table 6. Multivariate Association of HIV Infection and Medications with QTc Length.[a]

Characteristics	β Coefficient (95% CI)	*P* Value
a) Outcome = QTc Fredericia		
HIV positive	16.6 (2.7 to 30.5)	.019
Methadone	16.0 (1.9 to 30.1)	.026
Psychiatric medication	1.1 (−6.0 to 8.1)	.76
Antibiotics	11.5 (0.7 to 22.4)	.037
Antiretroviral therapy	−9.2 (−22.8 to 4.4)	.19
b) Outcome = QTc Bazett		
HIV positive	17.4 (0.9 to 33.9)	.039
Methadone	22.3 (5.6 to 39.0)	.009
Psychiatric medication	−0.04 (−8.4 to 8.3)	.99
Antibiotics	9.6 (−3.2 to 22.4)	.14
Antiretroviral therapy	−9.5 (−25.7 to 6.6)	.25

Abbreviation: CI, confidence interval.
[a]N = 261. β-Coefficients are the estimated difference in means (in milliseconds) between the 2 groups, adjusted for other factors (listed in this table) in multiple linear regression with QTc length as continuous outcome. *P* values are unadjusted for multiplicity.

the factors are listed in Table 5. Methadone use was associated with a higher odds of having prolonged QTc (OR = 4.58; $P = .01$), and use of ART was associated with a lower odds of QTc prolongation (OR = 0.35; $P = .04$) in HIV-infected patients. In contrast, gender, race/ethnicity, use of psychiatric medication and antibiotics, viral load, and CD4 count were not significantly associated with QTc prolongation, although low CD4 (<200 cells/mm^3 as a widely accepted and previously studied cutoff) showed a trend toward association. When we fitted a multiple logistic regression, adjusting for all covariates listed in Table 5 and HIV status jointly in the combined cohort (N = 261), only methadone was statistically significant, with the OR of 3.8 (95% CI: 1.3-11.0; $P = .01$ in Supplement) in the starting model and 4.3 (95% CI: 1.5-12.2; $P = .005$) in the final/parsimonious model as a sole independent variable.

As methadone is well known to be associated with prolonged QTc, we investigated whether the association between HIV status and QTc prolongation still held while controlling for use of methadone and the 3 other medication groups. Table 6 shows that QTc length (both by Bazett and Fridericia) was significantly longer in HIV-infected patients (approximately 17 milliseconds on average, $P < .04$) after accounting for the medications of interest. Finally, when we fitted all regression models with adjusting for diabetes, which showed imbalance between cases and controls in a sensitivity analysis, we reached similar results.

Our sensitivity analyses generally confirmed our primary findings reported earlier. First, methadone was associated with prolonged QTc with varying degrees of association and statistical significance. Second, HIV status demonstrated statistical significance when QTc was analyzed as continuous variable. Third, results were consistent including versus excluding patients on methadone. Interestingly, after excluding patients on methadone, HIV status showed a larger difference in prolongation (17 versus >20 milliseconds). See Supplementary Tables S3 and S4 for more details.

Discussion

This study investigated the prevalence of prolonged QTc segment on the 12-lead ECG in a diverse group of patients infected with HIV along with a comparator/control group of HIV-negative patients. Both groups were from the same hospital-based outpatient clinic and similar in terms of demographic characteristics and cardiovascular risk profiles. The QTc was longer overall in patients infected with HIV, and extreme prolongation (>500 milliseconds) was significantly more prevalent in the HIV group as well.

In the general population, estimates of drug-induced prolonged QTc vary due to different definitions of prolongation, and the ECG is often performed in a subset of patients who may not be representative of the general or HIV-infected patient

populations. For example, Riad et al used the EMRs at the University of Chicago to identify inpatients aged 18 or older with an ECG in the calendar year of 2011. Of 14 804 patients who met study criteria, 38% had prolonged QTc and 12% severe prolongation. The rate of QTc prolongation was significantly higher in both men and women who were receiving known QTc-prolonging medications compared to those who were not; however, both rates were relatively high although not unexpected as this was an inpatient population.[22]

The incidence of drug-induced TdP in the general population also varies in part because arrhythmia may be transient and it may not be detected or reported. Schwartz and Woosley reported an incidence ranging from 0.5% to 9% depending on which drug(s) a patient was taking.[3] Estimates of both prolonged QTc and TdP may be biased, for example, in studies of inpatients or participants who are undergoing treatment for specific medical conditions.

The prolongation of QTc interval has been studied in patients infected with HIV. Gili et al[10] investigated consecutive HIV-positive patients who were followed in a primary prevention clinic at 2 Italian institutions. Prolonged QTc was defined as >470 milliseconds in women and >450 milliseconds in men. Among the 351 patients, 7.4% had prolonged QTc.[10] There was no HIV-negative comparator group. In the HIV-HEART Study, Reinsch et al found prolonged QTc (>440 milliseconds in men and >460 milliseconds in women) in 22.8% of HIV-positive men compared to 3.9% of HIV-negative men and 12.1% compared to 1.8% in women.[9] The findings in this study are consistent with existing data showing greater prevalence of prolonged QTc in HIV-positive patients.

We observed in our study that use of any ART was associated with lower odds of prolonged QTc. The association of ART and QTc prolongation has been inconsistent in the literature, most likely due to variation in ART being used, CD4 count, and use of non-ART medications. Chinello et al in a nested case–control study found that QTc was prolonged in 9.8% of those infected with HIV. An increased risk of prolonged QTc was observed in patients prescribed nelfinavir (NFV), efavirenz (EFV), methadone, or cotrimoxazole or those who drank excessive amount of alcohol.[23] The Salmeterol Multicenter Asthma Research Trial (SMART) study reported that different boosted protease-based regimens had similar, minimal effects on QTc compared to NNRTI-based regimens.[6] A limitation of the SMART study is that methadone and other medications were not reported on. Reinsch et al found an association with smoking but not with ART or any co-medications.[9]

In a case–control study of Nigerian patients (45 HIV positive and 89 HIV negative), QTc was significantly longer in the patients infected with HIV with a nonsignificant trend to being longer in HIV-positive but ART-naive patients. The QTc shortened with increased duration of ART treatment and progressive reduction in viral load.[24] This suggests that the HIV virus itself, by infecting cardiac myocytes, can lead to fibrosis and conduction abnormalities and that suppression of viral replication using ART can potentially ameliorate this process. Additionally, of ART classes, the NNRTIs are most commonly implicated in QTc prolongation, and current first-line regimens as recommended[25] no longer include NNRTIs, potentially explaining our finding.

In the Gili et al's study, there was a higher prevalence of prolonged QTc in those with CD4 count below 200 cells/mm^3 at the time of the ECG (60% versus 24%) and with a nadir of CD4 count below 200 cells/mm^3.[10] In our study, we did not find an association between QTc prolongation and viral load or CD4 count.[10] In another study of 194 outpatients where 92.4% had undetectable viral load and a mean CD4 count of 553 cells/mm^3, neither viral load nor CD4 count was associated with prolonged QT.[8] The lack of association of CD4 or viral load with QTc prolongation in our study may reflect relatively well-controlled HIV in this cohort, with high CD4 counts and the majority of patients having undetectable viral load coupled with low statistical power.

Methadone is known to prolong the QTc interval in a dose-dependent fashion.[20] In our study, methadone was associated with higher odds of QTc prolongation (OR = 4.6; 95% CI: 1.4-15; $P = .01$) in HIV-positive patients, while OR was attenuated in HIV-uninfected patients (OR = 2.2; 95% CI: 0.2-25; $P = .53$), both with wide CIs, partly due to small sample sizes. In a cross-sectional study of opioid-dependent, HIV-infected patients on methadone maintenance therapy, 91 participants had an ECG recorded 24 hours after last supervised methadone administration. Both ART and other medications[26] that could prolong QT were noted. Prolonged QTc >450 was found in 36.3% and >500 in 3.2%. Higher methadone doses, being ART naive and chronic hepatitis C-induced cirrhosis, were associated with prolonged QTc.[11]

Use of psychiatric medications did not have a statistically significant association with QTc prolongation in our study. There is relatively a paucity of information available in the literature regarding psychiatric medications and their influence on QTc interval among patients infected with HIV. In a cross-sectional study of 6790 psychiatric inpatients over a 5-year period, 27.3% had an abnormal ECG with 1.6% having QTc $\geq$500 milliseconds and 0.9% determined to be drug induced. Compared to patients without prolonged QTc, those with prolonged QTc were more likely to have concomitant hypokalemia, hepatitis C, or HIV-positive status; 85.5% of those with drug-induced prolonged QTc had 2 or more factors associated with prolongation.[14] Also, we could not show that there was an association between QTc prolongation and antibiotics usage. There is relatively little information on the association between antibiotic use and prolongation of the QTc in patients infected with HIV. Certain antibiotics, however, have been well documented to carry a risk of QTc prolongation, particularly fluoroquinolones and macrolides. While there are less data comparing antibiotic-prescribing patterns in people with HIV compared to the general population, increased prevalence of bacterial infections including but not limited to pneumonia, often treated with these classes of antibiotics, could partially explain our findings. That we did not find an association between antibiotic use and QTc prolongation could be attributed to small sample size.

The 12-lead ECG was not commonly obtained in our clinic. The performance of an ECG has not been consistently a part of care for patients infected with HIV. In a cross-sectional study in the United Kingdom, there were 454 patients, of whom 81% were on a medication that could prolong QTc and 39% had drug interactions expected to increase QTc. However, only 30% of the 454 patients had an ECG. Having an ECG was associated with older age, diabetes, increasing number of medications, and gastric reflux.[27]

Despite package insert recommendations for ECG monitoring for patients on medications that can prolong the QTc interval such as some ART, methadone, and specific psychiatric or antibiotic medications, ECG monitoring is not specifically addressed in HIV treatment guidelines.[28] In the 2017 European AIDS Clinical Society Guidelines, an ECG is listed for initial assessment and subsequent visits with a note to "consider baseline ECG prior to starting ART associated with potential conduction problems."[29] Detection of ECG abnormalities such as left bundle branch block, atrial fibrillation, and left ventricular hypertrophy can provide information that can direct further evaluation as well as treatment to prevent heart disease and abnormalities impacting on a patient's cardiovascular health. As patients living with HIV are considered to be at higher risk of CVD,[30] the detection and management of both risk factors and manifest heart disease, along with a number of medications that HIV-infected patients take, have become a priority in the routine care of these patients.[31-33]

Limitations

This study has several limitations. First, our relatively small sample size precluded meaningful analyses of interaction and subgroups, comprehensive multivariable adjustment in regression, and main effects of factors with low prevalence. Of note, we did not find a statistically significant independent association between HIV infection and QTc when QTc prolongation was assessed as a binary variable, whereas we found a statistically significant association when QTc was analyzed as a continuous variable. Information and power loss is a common phenomenon when we categorize a continuous variable; thus, our findings are statistically explainable. The importance of fully powered study, interpretation along with cumulative evidence, and future validation should be emphasized, whenever feasible. Second, we were not able to confirm that QTc prolongation was acquired, as we did not have baseline tracings from patients prior to being infected with HIV and on potentially QTc prolonging medications. As such, they could have had a congenital form of QTc prolongation, although this is relatively rare. Third, ECGs were recorded using commercial machines with computer readings. The measurements used for this analysis were verified by a cardiologist; however, results may be less exacting than those obtained in core ECG laboratories. Fourth, the use of ART has rapidly changed over the years to where newer medications with fewer side effects are now the norm. We could not study any medications that came on the market after our study period.

Conclusion

In conclusion, CVD is becoming an increasingly important cause of morbidity and mortality in patients living with HIV. This study shows that one ECG parameter, prolongation of the QT interval, is more prevalent among patients infected with HIV, even after adjusting for the use of certain medications such as methadone, which has been shown to prolong the QT interval in previous studies as well as ours. Further research is needed to determine all causes for QT interval prolongation. Performing an ECG is noninvasive, relatively low cost, and can provide information relevant to the care of this patient population. Our study may add additional information to the body of existing literature that support baseline and routine monitoring by 12-lead ECG for patients infected with HIV.

Authors' Note

IRB Approval: St. Luke's–Roosevelt Hospital Center's Institutional Review Board determined that the protocol meets the qualifications for "exempt" status and the requirements for waiver of informed consent (IRB#: 11-008X).

Declaration of Conflicting Interests

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Supplemental Material

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