Indian Heart Journal 71 (2019) 434–439

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Review Article

QT prolongation in HIV-positive patients: Review article

Jing Liu [a], Sumit K. Shah [b], Indranill Basu-Ray [c, d, *], Julia Garcia-Diaz [e], Kainat Khalid [b], Mohammad Saeed [b, c]

[a] Baylor College of Medicine, Houston, TX, USA
[b] University of Arkansas for Medical Sciences, Little Rock, AR, USA
[c] Texas Heart Institute, Houston, TX, USA
[d] St. Francis Hospital, Memphis, TN, USA
[e] Ochsner Health System, New Orleans, LA, USA

ARTICLE INFO

Article history:
Received 5 July 2019
Accepted 25 November 2019
Available online 3 December 2019

Keywords:
HIV-positive
QT-interval
Torsades de pointes
Sudden cardiac death
Antiretroviral

ABSTRACT

Introduction: Antiretrovirals have immensely increased the average life expectancy of HIV-positive patients. However, the incidence of QT interval prolongation and other arrhythmias has also increased.
Methods: Pubmed and Google Scholar were searched for relevant literature published between 1990 and 2019.
Results and discussion: HIV-positive patients with high viral load, low CD4 count, chronic inflammation, and autonomic neuropathy can develop QT interval prolongation. Another factor prolonging QT interval includes exposure to the HIV transactivator protein, which inhibits hERG K (+) channels controlling IKr K (+) currents in cardiomyocytes. Protease inhibitors inhibiting the CYP3A4 enzyme can also lead to QT interval prolongation. QT interval prolongation can potentially be exacerbated by opioids, antipsychotics, antibiotics, and antifungals, the adjunct medications often used in HIV-positive patients. Hepatic insufficiency in seropositive patients on antiretrovirals may also increase the risk of QT interval prolongation.
Conclusion: Baseline and follow-up EKG in the susceptible population is suggested.

Key points

Question: Which factors may contribute to QT interval prolongation among HIV-positive patients?
Findings: Evidence from various epidemiological studies and case reports suggests that seropositive status, CD4 cell count, autonomic neuropathy, drugs inhibiting cytochrome P-4503A (CYP3A) enzyme, and hepatic dysfunction may be some of the factors leading to QT interval prolongation among seropositive patients.
Meaning: Management of HIV-positive patients should be approached with caution because seropositive status, CD4 cell count, autonomic neuropathy, cytochrome P-4503A (CYP3A) enzyme inhibiting drugs, and hepatic dysfunction may be some of the contributing factors for QT interval prolongation.

1. Introduction

Advances in the field of highly active antiretroviral therapy (HAART) have reduced HIV-associated morbidity and mortality, extending the mean life expectancy of HIV-positive patients.[1,2] However, this increased life expectancy has also led to an increase in the incidence of cardiovascular-associated mortality in

* Corresponding author: St. Francis Hospital, 6005 Park Avenue, 016841435, Memphis, TN, 38119, USA.
E-mail addresses: Jing.Liu@bcm.edu (J. Liu), sshah3@uams.edu (S.K. Shah), ibasuray@yahoo.com (I. Basu-Ray), jgarcia-diaz@ochsner.org (J. Garcia-Diaz), Kainat.Khalid@bcm.edu (K. Khalid), mohammas@bcm.edu (M. Saeed).

https://doi.org/10.1016/j.ihj.2019.11.259

this cohort.[3] QT interval prolongation is a precursor for fatal heart rhythm disorders, including ventricular fibrillation and torsades de pointes. QT interval prolongation is commonly encountered among seropositive patients. Patients with prolonged QT interval are relatively more prone to sudden cardiac death (SCD).[4,5] The mean rate of SCD was 4.5 times higher in the HIV-positive population as compared to the healthy population.[6] The associations between seropositivity, adverse effects of HAART, and heart rhythm disorder among HIV and AIDS patients are a major concern.[7–9]

While the exact mechanisms of fatal heart rhythm disorders leading to a higher rate of SCD among HIV-positive patients remain unknown, it has been hypothesized that alteration in cardiomyocyte channel currents and cardiac depolarization can cause QT interval prolongation.[10] Several case reports and epidemiological studies have reported a higher prevalence of prolonged QT interval among HIV-positive patients.[11,12] However, detailed literature and more comprehensive studies on this topic remain sparse. We aim to provide a critical review of the current literature to summarize and elucidate the different factors and mechanisms contributing to QT interval prolongation among HIV-positive adult patients in order to provide a better understanding of the phenomenon.

2. Methods

Our literature search strategy involved searching for articles on Pubmed and Google Scholar using the search terms “HIV and QT interval,” “AIDS and QT interval,” “HIV and QTc,” and “AIDS and QTc.” Articles describing and reporting evidence on QT interval prolongation in HIV and/or AIDS patients published after the year 1990 till 2019 were selected. Additional literature cited in the selected articles encompassing the topic of interest were also considered.

3. Results and Discussion

3.1. HIV viral load and CD4 count

Prevalence of QT interval prolongation is higher in patients with higher HIV viral load and lower CD4 cell count.[13] A cross-sectional cohort study involving 802 HIV-positive patients was conducted to identify the association between HIV seropositivity and QT interval prolongation. It was observed that HIV-positive patients exhibited a 20% higher prevalence of prolonged QT interval as compared to the HIV-negative population (12). A research team in Nigeria obtained similar results and concluded that HIV-positive patients had a higher prevalence of QT interval prolongation as compared to HIV-negative subjects.[14] Furthermore, the incidence of QT interval prolongation increased as the patients progressed toward developing acquired immunodeficiency syndrome (AIDS).[14] As stated earlier, lower CD4 cell count can be a contributing factor or even an independent factor for QT interval prolongation.[15] A prospective cohort study conducted in Thailand found that HIV-positive patients on combination antiretroviral (ARV) drugs and with lower CD4 cell counts had higher rates of QT interval prolongation.[16] A recent study conducted in 2017 involved 351 patients at two primary prevention clinics in Italy. Lower CD4 cell count (defined as CD4 count below 200 cells/ul) was consistently associated with prolonged QT interval. Also, the mean age was higher in patients with prolonged QT interval, as compared to those with QT in normal ranges.[17]

A retrospective cohort study conducted at the Bronx Lebanon Hospital suggested that seropositivity and a low CD4 cell count could potentially predispose patients to prolongation of QT interval. The study included a total of 5892 African-American HIV-positive patients who visited the clinic or were admitted to the hospital from 2009 through 2014. Out of 5892 HIV-positive patients, 2356 met the criteria for AIDS. Based on electrocardiogram (EKG) readings, almost 17% (1009 participants) of the study population was found to have a prolonged QT interval. The mean CD4 count of the study population was 124. Hence, it was concluded that lower CD4 cell count is also significantly associated with prolonged QT interval.[18]

3.2. Inflammation and autonomic neuropathy

The explicit mechanism through which HIV infection affects QT interval remains unknown. Several studies have proposed that chronic inflammation, persistent circulation of inflammatory components, and activated immune system cells are possibly the reasons for autonomic neuropathy, subclinical cardiomyopathy, or subclinical myocarditis, eventually leading to heart rhythm disorders.[19] Autonomic neuropathy is often observed among HIV-positive patients and possibly the cause for alterations in cardiac innervation and QTc prolongation. To assess the correlation, noninvasive cardiovascular reflex tests and EKGs were utilized to assess the autonomic functions and QT interval changes among 57 HIV-positive patients and 23 HIV-negative patients. Autonomic neuropathy and significantly longer QT interval were observed among 37 HIV-positive patients in comparison to the 23 HIV-negative patients. The study concluded that HIV-positive patients are more prone to alterations in autonomic functions and that QT interval is a reliable parameter for screening purposes. Since QT interval prolongation is a precursor of fatal ventricular arrhythmias, such patients should be managed with greater caution.[20]

3.3. Biochemical mechanisms

AIDS-associated cachexia has also been reported as a potential cause for heart disease in HIV-positive patients. EKG indices such as heart rate, QTc interval, T wave inversion, and ST-segment depression increased, while the systolic and diastolic blood pressure measurements fell significantly with the reduction in BMI in AIDS patients. Hence it was suggested that biochemical changes involved in cachexia and reduction in BMI might be contributing factors for QT interval prolongation in AIDS patients.[21] A deeper look into the pathways suggested that HIV infection significantly reduces outward K+ currents, ultimately leading to delayed ventricular repolarization.[22]

A study conducted in 2011 proposed a detailed molecular mechanism associating HIV infection with long QT syndrome. Human ether-a-go-go-related gene coding for hERG K (+) channels controls IKr K (+) currents in cardiomyocytes. Inhibition of these currents causes delayed repolarization of cardiomyocytes, leading to prolongation of QT interval. An HIV virus transactivator protein called HIV Tat protein also plays a pivotal role in this process. Cells incubated with HIV Tat protein had a considerably different recovery and inactivation time for hERG K (+) channels. Increasing the duration and dose of exposure to HIV Tat protein caused a significant inhibition of hERG K (+) currents. HIV Tat protein in vivo treatment of guinea pig cardiomyocytes reduced IKr currents and also caused prolongation of the action potential. Based on the aforementioned evidence, it was concluded that hERG K (+) currents and its protein expression are inhibited by HIV Tat protein possibly causing QT interval prolongation in HIV-positive patients.[23,24] Another study conducted a few years later published similar results after examining the effect of HIV Tat protein in rats. In HIV-1 infection, as the concentration of HIV Tat protein increased, there was an increase in the signal of Tat-mediated

pathways. It was clear that increased concentration of HIV Tat protein promoted bradycardia and QT interval prolongation.[25]

3.4. Medications

Adverse effects of medications and drug–drug interaction are also fairly common factors leading to arrhythmias, especially in patients who are on multiple-drug regimes.[26] Seropositive patients on HAART are frequently treated with adjunct antibiotics, antifungals, opiates, and several other medications for complications of AIDS or for collateral conditions observed in the cohort with AIDS. Collateral conditions may include drug abuse, psychiatric conditions, and chronic pain. Medications that are commonly used in seronegative and seropositive patients, which carry proarrhythmogenic properties, are listed in Table 1.

3.5. HAART

A study was conducted to investigate the association of QTc interval with HAART. Study subjects consisted of HIV-positive patients on HAART, HIV-positive HAART-naïve patients (HIV-positive patients but not on HAART), and a control group. A breakdown of the results showed that the prevalence of QT interval prolongation in seropositive patients on HAART was 18.2%, and it was 16.4% in seropositive HAART-naïve patients. Hence, it was concluded that HIV-positive patients on HAART have a higher prevalence of QT interval prolongation as compared to HIV-positive HAART-naïve patients. One of the possible explanations can be treatment with lopinavir (LPV) and zidovudine (ZVD) in seropositive patients.[31] Shavadia et al. noticed similar findings. They suggested that HAART predisposes HIV-positive patients to QTc interval prolongation as compared to the ART-naive controls (HIV-positive patients who were not taking antiretroviral therapy [ART]). The analyses were conducted after controlling for CD4 cell count and other confounding factors such as age, sex, comorbidities, risk factors for cardiovascular diseases, alcohol intake, and smoking status. However, it is difficult to draw an exact causal association and list the precise etiologies for prolonged QT interval.[32] These results illustrate variances between ARV and their adverse effects on QT interval. Further studies are needed for a better understanding of this issue.

Hyperlipidemia, hyperglycemia, and lipodystrophy are some of the adverse effects reported with the use of protease inhibitors (PIs). Hyperlipidemia is the most commonly observed adverse effect with a prevalence of almost 50% in patients on PIs.[33,34] Most PIs are potent inhibitors of cytochrome P-4503A (CYP3A) enzyme. Concomitant use of PIs with drugs that share the CYP3A metabolic pathway can potentially propel asymptomatic electrocardiographic abnormalities and precipitate dangerous arrhythmias.[35]

Several case reports and in vitro data have implied that PIs are a potential cause for QT interval prolongation and/or torsades de pointes. Ritonavir (RTV), a potent cytochrome P-4503A4 (CYP3A4) inhibitor, when used in combination with saquinavir (SQV) caused a significant prolongation of QT interval in studies comparing their effects in seropositive patients, as well as in healthy volunteers who served as a control group.[36] Anson et al. found an association between QTc prolongation and/or torsades de pointes with the use of PIs in 24 patients in the Food and Drug Administration's voluntary adverse event reporting system. It was suggested that LPV, nelfinavir (NFV), RTV, and SQV displayed dose-dependent blockage of hERG K+ channels in human embryonic kidney (HEK 293) cells in vitro. They further suggested that LPV induced blockage of repolarizing potassium current (IKr) channels in neonatal mouse cardiac myocytes lead to QTc prolongation.[37] Another study presented similar evidence by stating that atazanavir (ATZ) blocks hERG K+ channels, directly predisposing the subjects to QT interval prolongation.[38] Chinello et al. conducted multivariate analysis and found that NFV increases the risk of QTc interval prolongation (odds ratio [OR], 6.61; 95% confidence interval [CI], 1.79–24.38; $p < 0.005$) after adjusting for the plasma concentration of sodium, potassium, and calcium.[39]

Atazanavir, although a PI, has more desirable effects on serum lipid profile as compared to other PIs. It was administered to 21 patients and the results showed that QTc was prolonged 2 h after the first dose of ATZ (mean ± standard deviation 3.19 ± 8.0 ms; 95% CI, −0.47 to +6.85 ms; $p = 0.084$). However, the difference was not statistically different between QTc values and QTd values at baseline.[40] Moreno et al. conducted an observational study to investigate the prevalence and factors associated with prolongation of QT interval in asymptomatic HIV-infected patients. It was observed that the likelihood of QT prolongation was lower in patients treated with ATZ as compared to those treated with other PIs.[41] Results of this study concur with the results presented by the previous research studies.

Another study conducted by Zhang et al. examined the role of SQV/RTV combination on QT interval. The association was studied at therapeutic and supratherapeutic doses of the combination. It was reported that SQV/RTV combination administration in healthy patients and in HIV-infected patients is proarrhythmogenic and can potentially prolong QT interval. RTV and SQV, both administered

Table 1
Drugs with QT interval prolonging properties.

Class	Drug names
Antiviral	Ritonavir, Atazanavir [27], Saquinavir [28]
Opiates	Methadone, Levomethadyl [27], Oxycodone, Tramadol [29]
Antibiotic	Moxifloxacin, Levofloxacin, Ofloxacin, Gatifloxacin, Ciprofloxacin, Erythromycin, Azithromycin, Clarithromycin, Trimethoprim-Sulfamethoxazole [27], Metronidazole [26]
Antifungal	Ketoconazole, Fluconazole, Itraconazole, Voriconazole [27]
Antiemetic	Ondansetron, Granisetron, Dolasetron [27]
Antihistamine	Diphenhydramine, Terbinafine, Astemizole [27]
Antidepressant	Fluoxetine, Paroxetine, Sertraline, Citalopram, Escitalopram, Amitriptyline, Nortriptyline, Imipramine, Desipramine, Doxepin, Venlafaxine, Mirtazapine [27]
Antipsychotic	Haloperidol, Thioridazine, Clozapine, Risperidone, Quetiapine, Chlorpromazine [27]
Antiarrhythmic	Sotalol, Amiodarone, Quinidine, Procainamide, Disopyramide, Flecainide, Dofetilide, Dronedarone [27]
Diuretic, antihypertensive	Hydrochlorothiazide, Indapamide, Nicardipine [27], Furosemide [30]
Antianginal	Ranolazine, Bepridil [27]
Decongestant	Pseudoephedrine, Phenylpropanolamine [27]
Bronchodilator	Albuterol, Salmeterol, Metaproterenol, Terbutaline, Levalbuterol, Ephedrine [27]
Muscle relaxer	Tizanidine [27]
Nonsteroidal anti-inflammatory	Diclofenac, Celecoxib, Ketorolac [29]

individually, also have the potential to prolong QT interval. With the SQV/RTV combination, ART is frequently used to boost the therapeutic effect, but it can also impose an additional adverse effect on QT prolongation. Hence, it was concluded that HIV-positive patients should be pretested with EKG before initiating the SQV/RTV combination. Patients with a QT interval >450 ms should not be recommended this combination. A PR and QT interval prolongation "Warning and Precautions" insert was added to the SQV package based on the findings of this study.[42] A large-scale study by Soliman et al. recruited 3,719 study subjects from the Strategies for Management of Antiretroviral Therapy (SMART) study. In this study, 1,879 randomized participants received intermittent ART (drug conservation group) while the remaining received continuous drug therapy (viral suppression group). Multiple treatment regimes with PIs in combination with RTV were used in the drug conservation group. Another combination used in this group was PIs with nonnucleoside reverse transcriptase inhibitors (NNRTIs). QT interval was measured at 12 months and 24 months of follow-up in both groups. After careful investigation, it was concluded that all combinations with PIs showed a similar effect on QT interval prolongation, while NNRTI combination regimes did not show QT interval prolongation.[43] Dolutegravir, an integrase inhibitor and a novel HAART drug, has proven effectiveness against HIV with no significant adverse effects on cardiac repolarization, even with supratherapeutic doses.[44]

The mechanism for arrhythmogenic effects of PIs remains unclear, mostly because of the lack of large randomized controlled trials. Current data and literature suggest an association between HAART and QT prolongation, but these suggestions are mostly drawn based on the results from in vitro studies or studies with small sample size. None of the larger prospective studies have demonstrated any significant increase in QT interval following exposure to PIs. Ogunmola conducted a case-controlled study that involved HIV-positive patients on ART, HIV-positive patients not on ART, and HIV-negative subjects. They found that there was significant QT prolongation in HIV-positive patients both on ART and not on ART, as compared to the HIV-negative subjects. Although QT prolongation was relatively greater in HIV-positive patients on ART, it was not significantly different in comparison to the HIV-positive patients not on ART. These findings led researchers conclude that QT prolongation may not be entirely related to ART administration and that seropositivity may also play a significant role in QT interval prolongation.[45] This finding was similar to previous studies, which stated that ARV medications were not independently associated with prolonged QTc in HIV-infected patients.[46,47]

3.6. Methadone

The predisposition of HIV-positive patients to QT interval prolongation and torsades de pointes with methadone use is a well-established association.[48] Frequently, HIV-positive patients are also opioid drug abusers and require methadone maintenance therapy along with concomitant use of drugs that are potent inhibitors of CYP 3A4 (for example, PIs). It is of critical importance to meticulously evaluate HIV-positive and hospitalized patients before initiating PIs with methadone.

Case reports from other institutions reported similar results. Four HIV-positive patients developed prolonged QTc and torsades de pointes while being treated with ART and methadone.[49] Kao et al. conducted analyses on registry data to further explore this association. Study participants consisted of documented methadone-associated ventricular arrhythmias (1646 patients) and methadone-associated long QT interval (379 patients). It was reported that methadone is very commonly coadministered with ART, placing HIV-positive patients at risk of potentially fatal heart rhythm disorders.[50] Vallecillo et al. aimed to determine the prevalence and factors associated with long QTc interval in a cohort of seropositive opioid-dependent patients on methadone maintenance treatment. They found that almost 37% of seropositive patients on methadone therapy had prolonged QT interval. The adverse effect of QT interval prolongation can even further amplify if PIs are coadministered with methadone in patients with coexisting hepatic damage. Multiple regression analysis showed that methadone doses, chronic hepatitis C–induced cirrhosis, and ART-naïve status were all significantly associated with QT interval prolongation ($p = 0.005$, $p = 0.008$ and $p = 0.036$, respectively).[51] However, buprenorphine alone, a partial opioid agonist, is approved for opioid dependence treatment and has shown only a minimal effect on QTc prolongation.[52]

3.7. Other opioids

A prospective case-crossover study was conducted to examine the effects on QT interval in HIV-negative opioid-dependent patients. The control group was administered buprenorphine/naloxone (an antagonist of mu opioid receptors) combination while the intervention group was coadministered a combination of buprenorphine/naloxone with ARV drugs. Antiretrovirals included in the study were efavirenz (EFV), NFV, RTV, LPV/RTV combination, and delavirdine (DLV). The objective was to single out the cause for QT prolongation in opioid-dependent patients. Buprenorphine/naloxone alone did not cause any significant alteration in QT interval (despite the recent use of cocaine in some subjects). On the other hand, buprenorphine/naloxone in combination with ARV showed statistically significant prolongation of QT interval but with limited clinical significance. QT interval prolongation was the greatest with buprenorphine/naloxone combined with RTV and DLV. The explanation for QT interval prolongation stated that opioid receptor activity manipulation coupled with the CYP3A4 inhibition potential of RTV can precipitate fatal rhythm disorders, even in HIV-negative subjects.[52]

3.8. Adjunct medications

The advent of newer, more potent ARV drugs has caused a significant decrease in the incidence rate of HIV-associated opportunistic infections and cancers. Nevertheless, this is still not an uncommon phenomenon in the current era of HAART. There are circumstances when the HAART regimen fails due to drug resistance, poor patient adherence, or advanced disease status. Anti-infective, antineoplastic, and antihistamines are often recommended in addition to palliative support with HAART. Multiple studies and case reports have been published that suggest that coadministration of HAART with anti-infective, antineoplastic, antihistamine, and antipsychotic drugs changes myocardial action potential and potentially prolongs QT interval. Acquired QT interval prolongation increases the risk of torsades de pointes, a polymorphic ventricular arrhythmia that can quickly degenerate into ventricular fibrillation and cause SCD.[35]

Shimabukuro-Vornhagen et al. reported the case of a seropositive patient with pneumonia treated with a macrolide antibiotic who developed long QT syndrome and eventually, torsades de pointes.[53] Vallejo reported the case of an HIV-positive patient treated with intravenous cotrimoxazole and clarithromycin for HIV-associated opportunistic infections developing QT prolongation and ventricular arrhythmia.[54] Antipsychotic drugs are also commonly used to combat the mental conditions in HIV-infected and AIDS patients. Certain psychiatric medications such as haloperidol, clothiapine, phenothiazines, citalopram, and escitalopram

have been shown to induce QT prolongation in adult psychiatric patients with HIV infection or viral hepatic infection.[55]

3.9. Hepatic dysfunction

Hepatitis C coinfection is a common phenomenon observed among patients infected with HIV. Concomitant hepatitis C infection and liver damage further increase the risk of QT prolongation, most likely due to inadequate functionality of hepatic drug metabolism pathways.[56] Interestingly, both HIV and hepatitis C infections can be independent predisposing risk factors for prolonged QTc interval. A study reported that hepatitis C coinfection with HIV nearly doubled the risk of QTc interval prolongation (29.6% vs 15.8%, $p < 0.001$).[57] Unfortunately, many seropositive patients have coexisting liver damage and a history of alcohol abuse further exaggerating the adverse effects. A case report revealed that an HIV-positive woman on HAART with coexisting hepatitis B and hepatitis C infections developed prolonged QTc and torsades de pointes after initiation of methadone therapy for opioid dependence, even though she had no prior history of any cardiac abnormalities.[58] Hence, it is important to consider the possibility of hepatic coinfection or compromised hepatic function in all HIV-positive patients to prevent induction or worsening of QT interval prolongation.[16] EKG is a fairly simple yet effective screening test to screen the population susceptible to EKG abnormalities.[43]

4. Conclusion

HIV-infected individuals are at a high risk of developing QT interval prolongation and potentially fatal arrhythmias. The most likely reason for this may be the progression of the HIV disease status, presence of comorbidities, and coadministration of various medications with the potential to cause electrophysiological disturbances. Despite this, the frequency of QTc monitoring by EKG among HIV-infected patients remains low. It is of critical importance to consider the risk of QTc interval prolongation in patients with HIV infection. Although close monitoring with baseline and follow-up EKGs in seropositive patients may seem to be an unnecessary precaution, it should be considered in patients with multiple comorbidities treated with PIs and medications with proarrhythmic potential. Larger prospective cohort studies and trials are needed to further elucidate the mechanism of long QTc in HIV-positive patients.

Conflicts of interest

The authors have no conflict of interest.

References

1. The Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet*. 2008;372:293–299.
2. Andrieux-Meyer I, Calmy A, Cahn P, et al. Art Sequencing meeting September 22–23, 2011, Geneva, Switzerland. Preferred antiretroviral drugs for the next decade of scale up. *J Int AIDS Soc*. 2012;15:17986.
3. Palella Jr FJ, Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr*. 2006;43:27–34.
4. Schouten EG, Dekker JM, Meppelink P, Kok FJ, Vandenbroucke JP, Pool J. QT interval prolongation predicts cardiovascular mortality in an apparently healthy population. *Circulation*. 1991;84:1516–1523.
5. Elming H, Holm E, Jun L, et al. The prognostic value of the QT interval and QT interval dispersion in all-cause and cardiac mortality and morbidity in a population of Danish citizens. *Eur Heart J*. 1998;19:1391–1400.
6. Tseng ZH, Secemsky EA, Dowdy D, et al. Sudden cardiac death in patients with human immunodeficiency virus infection. *J Am Coll Cardiol*. 2012;59:1891–1896.
7. D'Ascenzo F, Cerrato E, Biondi-Zoccai G, et al. Acute coronary syndromes in human immunodeficiency virus patients: a meta-analysis investigating adverse event rates and the role of antiretroviral therapy. *Eur Heart J*. 2012;33:875–880.
8. D'Ascenzo F, Cerrato E, Appleton D, et al. Percutaneous coronary intervention and surgical revascularization in HIV Database (PHD) Study Investigators. Prognostic indicators for recurrent thrombotic events in HIV-infected patients with acute coronary syndromes: use of registry data from 12 sites in Europe, South Africa and the United States. *Thromb Res*. 2014;134:558–564.
9. Cannillo M, D'Ascenzo F, Grosso MW, et al. Heart failure in patients with human immunodeficiency virus: a review of the literature. *J Cardiovasc Med (Hagerstown)*. 2015;16:383.
10. Grandy SA, Brouillette J, Fiset C. Reduction of ventricular sodium current in a mouse model of HIV. *J Cardiovasc Electrophysiol*. 2010;21:916–922.
11. Reinsch N, Buhr C, Krings P, et al. German Heart Failure Network. Prevalence and risk factors of prolonged QTc interval in HIV-infected patients: results of the HIV-HEART study. *HIV Clin Trials*. 2009;10(4):261–268.
12. Puri R, Roberts-Thomson KC, Young GD. HIV and Long QT syndrome–cause or coincidence. *Int J Cardiol*. 2009;133(1):e9–e10.
13. Qaqa AY, Shaaban H, DeBari VA, et al. Viral load and CD4+ cell count as risk factors for prolonged QT interval in HIV-infected subjects: a cohort-nested case-control study in an outpatient population. *Cardiology*. 2010;117(2):105–111.
14. Sani MU, Okeahialam BN. QTc interval prolongation in patients with HIV and AIDS. *J Natl Med Assoc*. 2005;97(12):1657–1661.
15. Shaaban H, Qaqa A, Slim J, Perez G. The role of HIV Viral Load and CD4+ Cell Count in the prolongation of the QT interval in patients from an HIV outpatient clinic. *Int J Infect Dis*. 2010;14(SUPPL. 1):e79.
16. Wongcharoen W, Suaklin S, Tantisirivit N, Phrommintikul A, Chattipakorn N. QT dispersion in HIV-infected patients receiving combined antiretroviral therapy. *Ann Noninvasive Electrocardiol*. 2014;19(6):561–566.
17. 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 (Hagerstown)*. 2017;18(7):539–544.
18. Ayyadurai P, Shankar A, Burchfield H. Prolonged QT interval and ventricular tachycardia in a cohort of HIV infected African-American population. *J Card Fail*. 2016;22(Supplement 8):S58.
19. Kocheril AG, Bokhari SA, Batsford WP, Sinusas AJ. Long QTc and torsades de pointes in human immunodeficiency virus disease. *Pacing Clin Electrophysiol*. 1997;20(11):2810–2816.
20. Villa A, Foresti V, Confalonieri F. Autonomic neuropathy and prolongation of QT interval in human immunodeficiency virus infection. *Clin Auton Res*. 1995;5(1):48–52.
21. Okeahialam BN, Sani MU. Heart disease in HIV/AIDS. How much is due to cachexia? *Afr J Med Med Sci*. 2006;35(Suppl):99–102.
22. Brouillette J, Grandy SA, Jolicoeur P, Fiset C. Cardiac repolarization is prolonged in CD4C/HIV transgenic mice. *J Mol Cell Cardiol*. 2007;43(2):159–167.
23. 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(5):876–880.
24. Es-Salah-Lamoureux Z, Jouni M, Malak OA, et al. HIV-Tat induces a decrease in IKr and IKsvia reduction in phosphatidylinositol-(4,5)-bisphosphate availability. *J Mol Cell Cardiol*. 2016;99:1–13.
25. Brailoiu E, Deliu E, Sporici RA, Benamar K, Brailoiu GC. HIV-1-Tat excites cardiac parasympathetic neurons of nucleus ambiguus and triggers prolonged bradycardia in conscious rats. *Am J Physiol Regul Integr Comp Physiol*. 2014;306(11):R814–R822.
26. Armahizer MJ, Seybert AL, Smithburger PL, Kane-Gill SL. Drug-drug interactions contributing to QT prolongation in cardiac intensive care units. *J Crit Care*. 2013;28(3):243–249.
27. Fazio G, Vernuccio F, Grutta G, Re GL. Drugs to Be avoided in patients with long QT syndrome: focus on the anaesthesiological management. *World J Cardiol*. 2013;5(4):87–93.
28. Zhang X, Jordan P, Cristea L, et al. Through QT/QTc study of ritonavir boosted saquinavir following multiple-dose administration of therapeutic and supratherapeutic doses in healthy patients. *J Clin Pharmacol*. 2012;52(4):520–529.
29. Klivinyi C, Bornemann-Cimenti H. Pain medication and long QT syndrome. *Korean J Pain*. 2018;31(1):3–9.
30. Fernandes FM, Silva EP, Martins RR, Oliveira AG. QTc interval prolongation in critically ill patients: prevelance, risk factors and associated medications. *PLoS One*. 2018;13(6), e0199028.
31. Njoku PO, Ejim EC, Anisiuba BC, Ike SO, Onwubere BJ. Electrocardiographic findings in a cross-sectional study of human immunodeficiency virus (HIV) patients in Enugu, south-east Nigeria. *Cardiovasc J Afr*. 2016;27(4):252–257.
32. Shavadia J, Shah R, Yonga G, Patel R, Stebbing J, Nelson M. The influence of antiretroviral therapy on the QTc interval in an African cohort. *Clin Infect Dis*. 2012;54(3):448–449.
33. Reust CE. Common adverse effects of antiretroviral therapy for HIV disease. *Am Fam Physician*. 2011;84(2):154.
34. Manchanda T, Schiedel D, Fischer D, Dekaban GA, Rieder MJ. Adverse drug reactions to protease inhibitors. *Can J Clin Pharmacol*. 2002;9(3):137–146.
35. Fantoni M, Autore C, Del Borgo C. Drugs and cardiotoxicity in HIV and AIDS. Anti-retroviral medications. *Ann N Y Acad Sci*. 2001;946:179–199.

36. Hunt K, Hughes CA, Hills-Nieminen C. Protease inhibitor-associated QT interval prolongation. *Ann Pharmacother*. 2011;45(12):1544–1550.
37. Anson BD, Weaver JG, Ackerman MJ, et al. Blockade of HERG channels by HIV protease inhibitors. *Lancet*. 2005;365:682–686.
38. Han SN, Sun Xy, Zhang Z, Zhang LR. The protease inhibitor atazanavir blocks hERG K(+) channels expressed in HEK293 cells and obstructs hERG protein transport to cell membrane. *Acta Pharmacol Sin*. 2015;36(4):454–462.
39. Chinello P, Lisena FP, Angeletti C, Boumis E, Papetti F, Petrosillo N. Role of antiretroviral treatment in prolonging QTc interval in HIV-positive patients. *J Infect*. 2007;54:597–602.
40. Busti AJ, Tsikouris JP, Peeters MJ, et al. A prospective evaluation of the effect of atazanavir on the QTc interval and QTc dispersion in HIV-positive patients. *HIV Med*. 2006;7:317–322.
41. Moreno T1, Pérez I, Isasti G, Cabrera F, Santos J, Palacios R. Prevalence and factors associated with a prolonged QTc interval in a cohort of asymptomatic HIV-infected patients. *AIDS Res Hum Retrovir*. 2013;29(9):1195–1198.
42. Zhang X, Jordan P, Cristea L, Salgo M, Farha R, Kolis S. Thorough QT/QTc study of ritonavir-boosted saquinavir following multiple-dose administration of therapeutic and supratherapeutic doses in healthy participants. *J Clin Pharmacol*. 2012;52(4):520–529.
43. Soliman EZ, Lundgren JD, Roediger MP, et al. Boosted protease inhibitors and the electrocardiographic measures of QT and PR durations. *AIDS*. 2011;25(3):367–377.
44. Chen S, Min SS, Peppercorn A, et al. Effect of a single supratherapeutic dose of dolutegravir on cardiac repolarization. *Pharmacotherapy*. 2012;32(4):333–339.
45. Ogunmola O, Oladosu Y, Olamoyegun M. QTCinterval prolongation in HIV-negative versus HIV-positive subjects with or without antiretroviral drugs. *Ann Afr Med*. 2015;(4):169–176.
46. Fiorentini A, Petrosillo N, Di Stefano A, et al. QTc interval prolongation in HIV-infected patients: a case–control study by 24-hour Holter ECG recording. *BMC Cardiovasc Disord*. 2012;12:124.
47. 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(1):76–82.
48. Romero J, Baldinger SH, Goodman-Meza D, et al. Drug-induced torsades de pointes in an underserved urban population. Methadone: is there therapeutic equipoise? *J Interv Card Electrophysiol*. 2016;45(1):37–45.
49. Gil M, Sala M, Anguera I, et al. QT prolongation and Torsades de Pointes in patients infected with human immunodeficiency virus and treated with methadone. *Am J Cardiol*. 2003;92(8):995–997.
50. Kao D, Bucher Bartelson B, Khatri V, et al. Trends in reporting methadone-associated cardiac arrhythmia, 1997-2011: an analysis of registry data. *Ann Intern Med*. 2013;158(10):735–740.
51. Vallecillo G, Mojal S, Roquer A, et al. Risk of QTc prolongation in a cohort of opioid-dependent HIV-infected patients on methadone maintenance therapy. *Clin Infect Dis*. 2013;57(8):1189–1194.
52. Baker JR, Best AM, Pade PA, McCance-Katz EF. Effect of buprenorphine and antiretroviral agents on the QT interval in opioid-dependent patients. *Ann Pharmacother*. 2006;40(3):392–396.
53. Shimabukuro-Vornhagen A, Rybniker J, Zoghi S, et al. Acquired long QT syndrome and torsade de Pointes associated with HIV infection. *Case Rep Med*. 2010;(12).
54. Vallejo CN, Rodríguez PD, Sánchez HA, Tornos Mas MP, Ribera E, Soler Soler J. Ventricular tachycardia and long QT associated with clarithromycin administration in a patient with HIV infection. *Rev Esp Cardiol*. 2002;55(8):878–881.
55. Girardin FR, Gex-Fabry M, Berney P, Shah D, Gaspoz JM, Dayer P. Drug-induced long QT in adult psychiatric inpatients: the 5-year cross-sectional ECG Screening Outcome in Psychiatry study. *Am J Psychiatry*. 2013;170(12):1468–1476.
56. Petrosillo N, Lisena FP, Chinello P. QTc prolongation in human immunodeficiency virus-infected persons. *Arch Intern Med*. 2006;166(20):2288–2289.
57. Nordin C, Kohli A, Beca S, et al. Importance of hepatitis C coinfection in the development of QT prolongation in HIV-infected patients. *J Electrocardiol*. 2006;39(2):199–205.
58. Routhier DD, Katz KD, Brooks DE. QTc prolongation and torsades de pointes associated with methadone therapy. *J Emerg Med*. 2007;32(3):275–278.