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QTc interval prolongation in asymptomatic HIV – infected patients treated and untreated with antiretroviral therapy

Wydłużenie odstępu QTc u bezobjawowych pacjentów zakażonych HIV leczonych i nieleczonych antyretrowirusowo

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Summary

Aim: QTc interval prolongation has been found in HIV-infected patients. There are contradictory reports about the effects of antiretroviral drugs on QT interval duration. The aim of the study was to assess if the prolongation of the QTc interval depends on the antiretroviral treatment and other risk factors related to HIV infection.

Material/Methods: 283 adult HIV-infected patients treated in HIV Outpatient Clinic in Warsaw were enrolled in the prospective, single-centre study. Factors related to ART and HIV infection were collected. Electrocardiograms were performed for each patient and QTc interval duration was measured and corrected using Bazett's heart rate formula.

Results: Prolonged QTc interval was identified in 4.9 % HIV-infected patients (median age 34.5 years, 85% male, 89% HIV RNA<50 copies/mL). The average length of QTc interval in ART HIV(+) patients was 403 ms, in untreated HIV(+) subjects – 398ms and in the control group of healthy individuals – 400ms. ART regimen included PI in 47.4% cases, NNRTI in 24.1% and INI in 28.5% patients. The longest QTc interval was found in patients treated with the PI scheme – 408 ms, shorter with INI – 399ms and with NNRTI – 397ms. A multivariable analysis revealed that only older age and female gender were significantly associated with QTc prolongation.

Conclusions: In the group of young, asymptomatic HIV-infected patients with good immunovirological control, the prevalence of QTc prolongation was low – only 4.9% of subjects.

ARV treatment seem to have no significant influence on the QTc interval duration.

Keywords: **QTc prolongation • HIV infection • antiretroviral therapy**

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INTRODUCTION

The QT interval in the electrocardiogram (ECG) expresses the time required for the ventricular myocardium to depolarize and re-polarize. The prolongation of QTc often raises concern in clinical practice, as it can be followed, in rare cases, by the life-threatening polymorphic ventricular tachyarrhythmia called Torsade de Pointes (TdP). Torsade de Pointes manifests itself in palpitations, syncope, ventricular fibrillation and sudden cardiac death. The long QTc syndrome could be related to a rare genetic disorder or acquired due to internal or external factors, drugs as the most frequent cause. Acquired QT prolongation is usually associated with concomitant cardiovascular, metabolic, endocrine disease or electrolyte disorders [31, 35].

QT prolongation and its consequences are a serious clinical problem in the antiretroviral therapy (ART) HIV-infected and AIDS patients. Many antiretroviral drugs, even during registration, prompt concern as risk factors for prolongation to QT interval. People with HIV-infection undergo antiretroviral therapy their whole lives, every day, which has effects on health complications and requires the evaluation of interactions with additional drugs. Drug – drug interactions with medicaments metabolized by cytochrome P450 are considered to affect an increase in the concentration of some commonly used medicaments and to prolong the duration of QTc [2, 16]. Medicines associated with QTc prolongation include many different groups such as the following: antibiotics (clarithromycin, ciprofloxacin, mofloxacin, cotrimoxazole) antifungal (amphotericin, fluconazole, ketonazole, miconazole, clotrimazole), antimalarial (quinine, chloroquine, halophantine), antidepressants (fluoxetine, citalopram, paroxetine, venlaksafine, trazodone), antipsychotics (chlorpromazine, clozapine, haloperidol, quetiapine, risperidone, sertindol, thioridazine, ziprasidone), antihistaminic (astemizole, fexofenadine, loratidine), antiarrhythmics (amiodarone, sotalol, quinidine, dofetilide), others (methadone, sildenafil, cisapride, lithium, valproic acid, spironolactone, atropine, cocaine) [29, 34]. An updated list of drugs potentially prolong QT interval in the ECG is listed on the website www.qtdrug.org. The QT prolongation among HIV-infected people enhances due to frequently occurring cardiovascular disorders, such as damage the myocardium by HIV virus, local and systemic immuno-inflammatory reaction as well as autonomic neuropathy [5, 9, 14, 17, 28].

Currently, more than twenty drugs classified to different groups are used in antiretroviral therapy in Poland: nucleoside reverse transcriptase inhibitors – NRTI, non-nucleoside reverse transcriptase inhibitors – NNRTI, protease inhibitors – PI, integrase inhibitors – INI, fusion inhibitors – IF, CCR-5 co-receptor inhibitors [26]. The group of drugs most burdened with the possibility of prolonging the QT interval are protease inhibitors [2]. Currently, this class of drugs is increasingly being replaced by a new generation of integrase inhibitors that have similar efficacy but a better safety profile. However, in many clinical situations, PIs are still the drugs of choice in antiretroviral therapy widely used in Poland as well as in the world. The aim of the study was to assess if the prolongation of the corrected QTc interval depends on the antiretroviral treatment or/and other risk factors related to HIV infection.

METHODS

The study involved 295 adult HIV-infected patients treated in HIV Outpatient Clinic in Hospital for Infectious Diseases in Warsaw, who from January to December 2017 years held medical appointments and had an electrocardiogram (ECG) performed during the visit. The study was conducted as part of the POLCA (Polish Observational Cohort of HIV/AIDS Patients) project with the consent of the Bioethical Commission at Warsaw Medical University No. 111/2010. Prior to enrollment, each patient agreed to participate in the study. For ECG monitoring qualified asymptomatic successfully treated patients with antiretroviral (VL HIV RNA <50 copies/ml) for at least six months, without any significant immunodeficiency (with CD4 counts> 350 cells/uL) in clinical stage A according to the CDC (Centers for disease Control and Prevention) [6] and who were treated with the recommended PTN AIDS (Polish AIDS Society) antiretroviral therapies: 2NRTI + 1PI/r or 2NRTI + 1NNRTI or 2NRTI + 1INI [12].

Physical examination was carried out in every patient and they were asked about concomitant comorbidities, current medications and dietary supplements. Medical documentation and available laboratory tests were verified.

The reference group consisted of 30 HIV infected patients who have not yet started antiretroviral treatment and the control group of 30 healthy people not infected with HIV, who came to the Clinic to perform a diagnostic test for HIV infection.

The study excluded patients with chronic diseases, especially cardiac patients with neurovegetative symptoms who were taking other drugs potentially prolong the QT interval and those who in the past have observed electrolyte abnormalities. Patients with HBV and HCV co-infection were not excluded from the study group. The following data was analyzed: the patient's age of ECG performing, sex, coinfection of hepatitis C based on anti-HCV serology and the presence of HCV-RNA in serum and hepatitis B based on the presence of HBsAg antigen, current cART treatment regimen and HIV viral load (VL HIV RNA).

ELECTROCARDIOGRAM (ECG)

In all subjects, 12-lead ECGs were performed after 15 minutes of rest. The AsCARD MrSilver ver 2.24 was used for the study with a write speed of 25 mm/s and a sensitivity of 10 mm/mV. The length of the QT interval and the corrected QTc interval were measured automatically according to Bazett's heart rate formula QTc = QT/(RR)1/2, where RR is the interval between two waves and verified manually by the researchers. The length of up to 440 ms in men and up to 460 ms in women was accepted as the QTc interval norm [21].

STATISTICAL ANALYSIS

Statistical analyzes were performed using the SAS program, version 9.1. The correlation between discrete and continuous variables was evaluated by chi-square, t-student and ANOVA. Parametric data was expressed as mean ± standard deviation. In the analysis of potential risk factors of the QTc prolongation, the linear stepwise backward regression model was used, guided by the probability p value. The p value of 0.05 was considered statistically significant.

RESULTS

Characteristics of patients

283 HIV infected patients and 30 people from the control group were included in the analysis. Twelve people were excluded from further evaluation due to irregularities found in the ECG record. These were the right bundle branch block, WPW syndrome, left bundle branch block, paroxysmal atrial fibrillation. The basic demographic and clinical data of HIV-infected patients are shown in Table 1.

In the study, 253 (100%) were successfully treated with antiretroviral therapy (HIV RNA <50 copies/mL. All subjects were treated with two NRTIs as a third element of combination antiretroviral therapy PI received 120 (47.4%), NNRTI 61 (24.1%) and INI 72 (28.5%) patients. The percentage share of the third ART component in the group of patients treated with antiretroviral therapy reflects the real proportions of therapeutic regimens used in the HIV Outpatient Clinic in Warsaw.

Prolongation of the QTc interval

The average length of QTc interval in antiretroviral treated patients was 403 ms. In the reference group – in untreated HIV-infected subjects – 398 ms, and a control group of healthy individuals 400 ms. Among patients treated with cART, the longest QTc interval was found in patients treated with the PI scheme – 408 ms, shorter in the group with INI – 399 ms and with NNRTI – 397 ms. However, these differences were not statistically significant.

The prolongation of the QTc interval> 440ms for men and> 460ms for women was found in 4.9% of all HIV-infected persons and 5.1% of patients on ART. Most often, these changes occurred in patients receiving PI (6.6%). There were no statistically significant differences between patients receiving different therapeutic regimens. In the group of patients receiving NNRTI and INI, QTc prolongation occurred with a similar frequency as in the reference and control groups. The data is shown in Table 2. Only one patient was found QTc interval > 500 ms and was treated with PI.

Factors affecting the QTc interval

The results of univariate and multivariate analysis of various parameters associated with QTc interval prolongation in HIV-infected patients are shown in Table 3. Only age (p <0.001) and gender (p = 0.014) affected the QTc interval length. Although in the univariate analysis, HCV infection significantly influenced the prolongation of the QTc interval, multivariate analysis did not confirm these. No significant effect of particular classes of antiretroviral drugs (PI or NNRTI or INI) on QTc prolongation in this analysis was observed.

DISCUSSION

Valid values of the QT interval in the general population are different in men and women, and they change with age. A longer interval among women and the elderly is regarded as a physiological norm. [22]. QT prolongation is often a side effect of different drugs used. There are many recommendations for monitoring the QTc interval during various therapeutic treatments [3, 11], but this issue has not been widely studied in HIV-infected antiretroviral treated patients. A few reports come from the era of older generation drugs, often no longer used in Poland [2]. Therefore, it is essential to study the incidence of this complication during the currently used modern antiretroviral drugs.

Table 1. Characteristics of 283 HIV-infected patients

Feature	Result
Age*, years [median (IQR)]	34.5 (11)
Sex, men [n (%)]	242 (85)
Route of infection: MSM/IDU/HTR [n (%)]	158(56) / 68(24) / 57(20)
VL HIV RNA < 50 copies/ml [n (%)]	253 (89)
VL HIV RNA >50 copies/ml [n (%)]	30 (11)
CD4 >350 cells/uL [n(%)]	283 (100)
HCV (+) infection [n (%)]	65 (23)
HBV (+) infection [n (%)]	10 (3.5)
HIV (+) not on ART [n (%)]	30 (11)
HIV (+) on ART [n (%)]	253 (89)
NRTI	253 (100)
– 3TC or FTC [n (%)]	253 (100)
– TDF or TAF [n (%)]	175 (69.2)
– ABC [n (%)]	78 (30.8)
PI [n (%)]	120 (47.4)
– ATV/r [n (%)]	28 (23.3)
– LPV/r [n (%)]	33 (27.5)
– DRV/r or DRV/c [n (%)]	59 (49.2)
NNRTI [n (%)]	61 (24.1)
– EFV [n (%)]	38 (62.3)
– RPV [n (%)]	23 (37.7)
INI [n (%)]	72 (28.5)
– RAL [n (%)]	17 (23.6)
– DLV [n (%)]	17 (23.6)
– EVG/c [n (%)]	38 (52.8)

3TC – lamivudine, FTC – emtricitabine, TDF – tenofovir disoproxil, TAF – tenofovir alafenamide, ABC – abakavir, ATV/r – atazanavir boosted with ritonavir, LPV/r – lopinavir boosted with ritonavir, DRV/r – darunavir boosted with ritonavir, DRV/c – darunawir boosted with cobicistat, EFV – efavirenz, RPV – rilpivirine, RAL – raltegravir, DLV – dolutegravir, EVG/c – elvitegravir boosted with cobicistat. MSM – men who have sex with men IDU – injecting drug users, HTR – heterosexual; * age at the time of ECG

For the first time in 1997, Kocheril et al. noticed a significantly higher percentage of patients infected with HIV and AIDS with QT prolongation> 440ms, compared with non-infected patients 28.6% vs 7% [13]. The works of other authors confirmed the increased percentage of patients with prolonged QTc interval among HIV(+) patients compared to the general population [23, 28, 30]. In the present study, the percentage of people infected with HIV with prolonged QTc interval above normal was significantly lower and consists only 4.9%. The incidence of QTc prolongation in the study group was similar to that of the healthy group – 3.3%. Similar results were obtained by French researchers who evaluated QTc in a comparable age and sex group showing QTc prolongation only in 2.3% of treated ART and 2.4% of HIV-infected untreated ART. Among those treated with antiretrovirals, 39% had a therapeutic scheme with PI/r [1].

Older patients, with a median age of 46.3 years, were studied by Moreno et al. They were patients with a more advanced disease, at 27.8% of the clinical stage of AIDS according to CDC. QTc prolongation in these individuals was demonstrated in as many as 12.4% of HIV-infected patients treated with antiretrovirals (ARV) [19], whereas Chinello et al. showed QT prolongation in the HIV (+) individuals in 9.8% of first-generation antiretrovirals, i.e. efavirenz, nelfinavir, zidovudine and other drugs affecting the QT interval, e.g. cotrimoxazole or methadone [8]. It seems that a significant range of the prevalence of QTc prolongation in HIV-infected patients resulted from the selection of the study group. A significantly higher frequency was demonstrated in studies in which the study group was older and had numerous clinical burdens such as a large number of drugs, including known effects on QT interval.

Table 2. QTc interval in groups of subjects

Groups of subjects	N	QTc interval (mean ± SD) ms	QTc >440 ms in men and QTc >460 ms in women; N(%)	QTc > 500 ms N (%)
HIV (-)	30	400±20	1 (3.3)	0
HIV (+) not on ART	30	398±23	1 (3.3)	0
HIV (+) all on ART	253	403±29	13 (5.1)	0
HIV(+) treated with PI	120	408±36	8 (6.6)	1 (0.8)
HIV(+) treated with NRTI	61	397±22	3 (4.9)	0
HIV(+) treated with INI	72	399±18	2 (2.7)	0

Although previous work suggested that antiretroviral treatment, especially with protease inhibitors, increase the risk of QT prolongation in HIV(+), the most recent studies do not confirm that [1, 7, 12, 32]. In an earlier in vitro study, four PIs of nelfinavir, lopinavir, ritonavir and saquinavir have been shown to prolong the QT interval act by blocking hERG (Human Ether-a-go-go-related Gene) I_{Kr} potassium channel [2]. Those drugs are mostly not currently used in Poland, which probably contributed to QTc prolongation rarely observed in our group of patients treated with ARV. Also, in the presented work, it has not been confirmed that current modern ARV therapy, including PI of the new generation, has a significant impact on the QTc interval. These studies were carried out in a particular group of HIV-infected – asymptomatic patients without comorbidities, relatively young in most men.

However, it seems that HIV(+) patients should be under professional care and monitored with subsequent ECG. Aside from antiretroviral therapy that must be used every day for their whole lives, HIV patients need to take anti-inflammatory medicine in acute infections, as well as the prevention of primary or secondary opportunistic diseases such as antibiotics from the group of macrolides, quinolones, sulfonamides, antiviral, antifungal, antiparasitic drugs that affect the prolongation of QTc [15]. Moreover, a serious and demanding problem is the frequent use of antidepressants or antipsychotics that prolong the QTc interval [3, 4]. Some HIV – infected patients remain on methadone therapy. Methadone is known to affect the prolongation of QT interval [11]. The current, effective antiretroviral therapy allows HIV patients to have a life expectancy similar to that of the general population [27]. These patients thus become susceptible to age-related diseases, such as

Table 3. Univariate and multivariate analysis of factors affecting the QTc interval

Factors	Level (reference group)	Average QTc difference from reference level (univariate analysis)*	95% confidence intervals	p	Average QTc difference from reference level (multivariable analysis)*	p
Group of subjects	HIV(+) patenients on ART	+5 ms	(-8)-(+17) ms	0.655	No statistical significance	>0.050
	HIV(+) patients not on ART	0 (reference level)	-	-	No statistical significance	>0.050
	HIV(-) subjects*	+2 ms	(-15)-(+18) ms	0.969	-	-
Class of ART	PI	+11 ms	(+0)-(+22) ms	0.049	No statistical significance	>0.050
	INI	+2 ms	(-7)-(+11) ms	0.931	No statistical significance	>0.050
	NNRTI	0 (reference level)	-	-	No statistical significance	>0.050
Gender	Women	+11 ms	(+2)-(+20) ms	0.020	No statistical significance	>0.050
	Men	0 (reference level)	-	-	+11ms	0.014
Age [years]	(QTc increase for each additional year of life)	+1 ms for a year of life	-	<0.001	+1ms for a year of life	<0.001
HCV Infection	HCV(+) patients	+10 ms	(+1)-(+20) ms	0.040	No statistical significance	>0.050
	HCV(-) patients	0 (reference level)	-	-	No statistical significance	>0.050

*HIV(-) subjects were used only to compare with HIV(+) group treated and untreated. HIV(-) persons were not included in other analyzes

cardiovascular diseases, diabetes, chronic kidney diseases, osteoporosis and malignancies [33]. The presence of co-morbidities can increase the number of prescribed medications, and drug interactions may intensify the impact of the various side effects, including the prolongation of QT interval. In HIV-infected subjects, simultaneously using several drugs that inhibit I_{Kr} current or with potent cytochrome P450 inhibitors can lead to a significant prolongation of the QT interval and severe cardiac arrhythmia [16].

There is no universal limit value of QTc associated with an increased risk of TdP, but in patients with drug-induced QT prolongation, almost all ventricular arrhythmic events occurred with QTc> 500ms [20, 35]. In the presented study, only one 46-year-old female patient treated with LPV/r from the PI group had QTc prolongation to 552 ms. She did not report any clinical symptoms during ARV therapy. In that case, the PI was replaced with an integrase inhibitor (INI) – dolutegravir a potentially neutral effect on repolarization of the myocardium, which is not metabolized by cytochrome P450. In clinical practice, arrhythmia caused by QT prolongation is rarely associated with the use of only one drug. Withdrawal symptoms such as palpitations, fainting or sudden death are multifactorial and typically result from the use of two or more drugs affecting this same pathway, further electrolyte disturbances or genetic predisposition [31, 35].

According to earlier studies as well as our study, the independent risk factors for QT prolongation were older age and female gender, similar to the general population [7, 28, 32]. Patel et al., Reinsch et al., and Charbit et al. also noted that the risk of prolongation of the QT interval increases with the duration of an HIV infection, hypertension, diabetes, and HCV co-infections [7, 25, 28].

Although a univariate analysis in our study showed a similar relationship, no significant effect of HCV co-infection on QT prolongation was confirmed in a multivariate analysis. The impact of HCV infection and/or advanced liver disease on the QT interval requires in-depth studies, because some authors have shown that QTc is prolonged in patients with cirrhosis regardless of its etiology [10]. In the present study, we did not include the severity of liver fibrosis in the course of co-infection with HCV.

The limitation of our study is the lack of ECG assessment before the inclusion of ART, which made it impossible to exclude people with congenital long QT syndrome. However, such disorders are quite rare in the population. No laboratory tests were performed on the ECG day. Possible electrolyte abnormalities were assessed only clinically during the medical examination and retrospectively by analyzing the medical documentation.

CONCLUSION

In the group of young, asymptomatic HIV infected patients, with good immunovirological control, the prolongation of the QTc interval was rare and concerned only 4.9% of the subjects. There was no evidence that the use of antiretroviral therapy, or any class of drugs PI or NNRTI or INI, could independently predispose to QT prolongation. However, other non-HIV related risk factors, such as older age and female gender, may significantly increase the risk of QT interval prolongation similar to that of the general population. ECG monitoring seems particularly indicated in the group of elderly HIV(+) patients treated with antiretroviral therapy, with different co-morbidities and/or taking other drugs with a known effect on the prolongation of the QT interval.

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