https://doi.org/10.35839/repis.5.3.935

Frequency of QTc interval prolongation in HIV-infected adults from Paraguay in 2020

Frecuencia de prolongación del intervalo QTc en adultos infectados con VIH de Paraguay en 2020

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Abstract

Introduction: The prolonged QTc interval predisposes to serious arrhythmias. Various medications, including antiretrovirals, can prolong it. The objectives were to determine the demographic, clinical characteristics and the frequency of the prolonged QTc interval in patients with HIV. **Methods**: We conducted a prospective, observational study with a control group. Men and women, over 18 years of age, with HIV infection, who attended the National Hospital (Itauguá, Paraguay) during 2020, were included. Medical students acted as a control group. All subjects who did not give their consent and those with arrhythmias were excluded. Demographic, clinical, laboratory variables and 12-channel electrocardiogram at rest were measured. The study was approved by the Ethics Committee of the Private University of the East (Paraguay). **Results**: A total of 39 HIV patients and 39 healthy controls was entered to the research. The mean age of the cases was 37 ± 11 years, being 59% male. The most frequent comorbidity in the cases was obesity (7.6%). The mean values of urea, creatinine, K, Ca and Mg in the cases were in the normal range. Prolonged QTc was detected in 18% of the cases and in 0% of the controls. The subjects with the electrocardiographic alteration were all on antiretroviral and multiple antibiotic treatment known to be associated with prolonged QTc. **Conclusion**: the frequency of prolonged QTc in HIV patients was 18% and in healthy controls it was 0%. Regular monitoring of the electrocardiogram is recommended in HIV patients receiving drugs that prolong the QT interval.

Keyword: long QT syndrome, electrocardiography, HIV, antiretrovirals.

Resumen

Introducción: el intervalo QTc prolongado predispone a arritmias graves. Diversos medicamentos, entre ellos los antirretrovirales, pueden prolongarlo. Los objetivos fueron determinar las características demográficas, clínicas y la frecuencia del intervalo QTc prolongado en pacientes con VIH. **Métodos**: estudio observacional, prospectivo, con grupo control. Se incluyeron varones y mujeres, mayores de 18 años, portadores de infección por VIH, que acudieron al Hospital Nacional (Itauguá, Paraguay) durante 2020. Actuaron como grupo control los estudiantes de Medicina. Se excluyeron todos los sujetos que no dieron su consentimiento y los portadores de arritmias. Se midieron variables demográficas, clínicas, laboratoriales y electrocardiograma de 12 canales en reposo. El estudio contó con la aprobación del Comité de Ética de la Universidad Privada del Este (Paraguay). **Resultados**: ingresaron al estudio 39 pacientes con VIH y 39 controles sanos. La edad media de los casos fue 37 ± 11 años, siendo 59% del sexo masculino. La comorbilidad más frecuente en los casos fue la obesidad (7,6%). Los valores medios de urea, creatinina, K, Ca y Mg en los casos se hallaban en rango normal. Se detectó 18% de QTc prolongado en casos y 0% en los controles. Estos sujetos con alteración electrocardiográfica se hallaban todos en tratamiento antirretroviral y antibiótico múltiple de conocida asociación con QTc prolongado. **Conclusión**: la frecuencia de QTc prolongado en pacientes con VIH fue del 18% y en controles sanos fue del 0%. Se recomienda el control periódico del electrocardiograma en pacientes con VIH en tratamiento con fármacos que prolongan el intervalo QT.

Palabras clave: síndrome de QT prolongado, electrocardiografía, VIH, antirretrovirales.

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Reception date: january 30, 2021
Approval date: may 23, 2021

Quote as: Real-Delor RE, Brítez-Calderón SJE, Carballo-Báez VV, Cuevas-Machuca DN, Díaz-Fretes SA, Escurra-Torres MA, Escurra-Torres RD, García-Almirón DM, González-Cantero EM, Halke-Saiz JR, Larrea-Alarcón AL, Medina-Valdez PN, Mendoza-Ayala KN, Orrego-Martínez AE, Ortiz-Martínez JL, Pirelli-Cubas GJ, Tobal-Gómez ME. Frecuencia de prolongación del intervalo QTc en adultos infectados con VIH de Paraguay en 2020. Rev. Peru. Investig. Salud. [Internet]; 5(3): 173-179. Available from: http://revistas.unheval.edu.pe/index.php/repis/article/view/935

Introduction

Ventricular depolarization and repolarization are represented on the electrocardiogram (ECG) by the QT interval (1). The duration of the QT interval can have circadian, age and gender variations. But the most influential factor is the heart rate, hence this interval must be corrected: it is the corrected QT interval (QTc) (2). The QTc should not be greater than 0.45 sec in men and 0.47 sec in women, otherwise it is called long or prolonged QT syndrome (LQTS) (3). Other authors consider SQTP when at least 2 ECGs with QTc> 0.50 sec are detected (4,5). Any new QTc prolongation> 0.30 sec with respect to the baseline ECG should attract attention and when it is> 0.60 sec, therapeutic measures should be taken (6). The risk of adverse cardiac events increases exponentially with QTc prolongation: for every 0.10 sec increase in QTc there is a 5% increase in the risk of arrhythmic events. Measurement of QT dispersion is cumbersome and does not provide additional data on the risk of arrhythmias. However, a change in the morphology of the T wave and the variation of the Tpeak / Tbase index are better predictors of arrhythmias (7).

PCOS is a disease characterized by prolonged ventricular repolarization time and predisposition to life-threatening ventricular arrhythmias. Long QT is related to the appearance of early postpotentials and increased dispersion of the QT period in the different layers of the cardiac myocardium (8). The

cause of PCOS can be congenital or acquired. The congenital form is genetic in origin and is quite rare. But acquired is much more frequent and is secondary to the action of drugs, fluid and electrolyte disorders (hypokalaemia, hypomagnesemia, and hypocalcemia), ischemic heart disease, cardiomyopathies, extreme bradycardia, subarachnoid hemorrhage, hypothyroidism, acidosis, and AIDS. Therefore, many acquired forms of PTS are preventable (9).

The drugs involved are diverse: antiarrhythmics, antibiotics, antivirals, azole antifungals, antimalarials, antineoplastics, antiemetics, prokinetics, antipsychotics, antidepressants, among others (8). The combination of macrolides and quinolones is common but is not recommended due to its effects on QTc prolongation (6). The Arizona Center for Education and Research on Therapeutics (AZCERT) initiative to register drugs related to QTc prolongation has led to updated lists of drugs with this effect. These lists are freely available on the internet and are widely used in research and clinical practice. The drugs are classified into 4 groups: prohibited in SQTP, known effect on QTc, probable effect on QTc and effect on QTc conditioned by other factors (10).

Although many drugs prolong the QT interval, tip torsion is a rare event: 4 per 100,000 patients. But this frequency increases when risk factors are added. The following conditions increase this risk: heart failure, structural heart disease, bradycardia, hypokalaemia, hypomagnesaemia, hypocalcaemia, subclinical ion channel mutations, high doses of drugs, old age, metabolism inhibitors, combination of two or more drugs that prolong blood pressure. QT interval (2). The female sex, due to the effect of estrogens, generates more susceptibility to QTc prolongation. Caucasians are more likely than others to suffer from PCOS. HIV infection, especially in the AIDS stage, is another predisposing factor for PCOS due to various factors including the side effects of antiretrovirals (11).

This research was justified because according to data from PRONASIDA, HIV infection in Paraguay shows a progressive annual increase reaching the epidemic range (12). Current treatment for HIV infection in Paraguay includes 3 drugs: efavirenz 600 mg / emtricitabine 200 mg / tenofovir disoproxil 245 mg. The frequency of ECG alterations in AIDS patients is between two and three times that of the general population, which increases cardiovascular risk in these patients (13-15). Although the SQTP in patients with HIV is multifactorial, the ECG is capable of detecting potentially fatal abnormalities (5,16,17). This is a rapid, non-invasive diagnostic method with a high predictive value for cardiovascular complications (13,14). Continuous measurement of the QTc interval is recommended in patients receiving antiretrovirals (18). A similar study in patients from Medical Clinic PCOS in some patients with HIV (19), which is why this investigation focused on these subjects.

The objectives were to determine the frequency of PCOS in HIV-positive adult patients of the Medical Clinic Service of the National Hospital (Itauguá, Paraguay) in 2020, to describe the demographic (age, sex), clinical (BMI, clinical stage of infection by HIV, type and duration of antiretroviral treatment, other medications, comorbidities) and laboratory tests (serum urea, creatinine, potassium, calcium and magnesium). In addition, detail the drugs administered according to the AZCERT list: known association, possible association, conditional association. Healthy subjects were used to use the frequency of QTc interval alterations in them as a population parameter in the country.

Methods

An observational, descriptive, prospective, cross-sectional design was applied, with a control group. The study population consisted of men and women, over 18 years of age, HIV carriers who attended the Medical Clinic Service of the National Hospital (Itauguá, Paraguay) between March and November 2020. As a control group, ECGs were performed at different Medicine students. This sample served as a frequency parameter for congenital SQTP in the country.

The inclusion criterion was current 12-channel ECG without technique artifacts. Patients with atrial fibrillation, electrical conduction disorders, preexcitation syndrome, pacemaker rhythm, complete right or left bundle branch blocks, left ventricular hypertrophy by voltage criterion were excluded. All these criteria made it possible to exclude those patients with PTSD induced by non-drug factors.

A non-probabilistic sampling of consecutive cases was used. Demographic variables (age, sex), clinical variables (BMI, clinical stage of HIV infection, type and duration of antiretroviral treatment, other medications, comorbidities) were determined. In addition, laboratory data (serum urea, creatinine, K, Ca and Mg).

The QT interval and the RR interval were measured in lead D1, aVL, V5 and V6 using the average of the values obtained in at least 3 cardiac cycles. In the case of sinus arrhythmia, the average of three measurements in the same lead was used. The end of the T wave was determined by the point at which it meets the isoelectric baseline or by the intersection of an extrapolated line on the isoelectric line and the tangent line that touches the end of the T wave at the most extreme point. lower. To obtain the corrected QT, Bazett's formula was applied, in which the QT interval measured in seconds is divided by the square root of the preceding RR time expressed in seconds. Prolonged QTc was considered if ≥0.45 sec in men and ≥0.47 sec in

women (1,3).

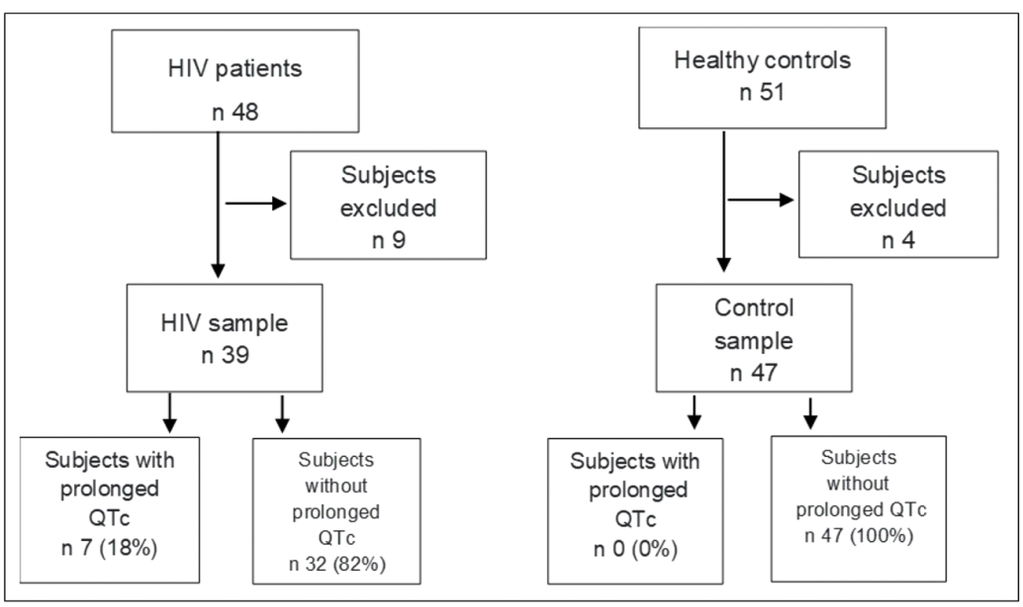
For convenience, all subjects who met the inclusion criteria in the planned study period were incorporated. Descriptive statistics were performed with the Epi Info 7 © program. The qualitative variables were expressed in frequencies and percentages, while the quantitative variables in measures of central tendency and dispersion.

Ethical aspects: the confidentiality of personal data was respected. Patients or dependents could voluntarily decide to participate in the research. No type of discrimination was made when selecting the subjects. This research did not involve harm to the patients or cost them. The patients were informed in their native language of the procedures to be carried out and signed an informed consent. When each case of PCOS was detected, the treating physician was immediately informed so that he could take the pertinent measures. The authors declare that they have no conflicts of commercial interest. The protocol was evaluated and approved by the Research Committee and the Ethics Committee of the Private University of the East (Paraguay).

Results

Between March and December 2020, 39 patients with HIV and 47 healthy controls were included (graphic 1).

Graphic 1. Flowchart of sample inclusion



The subjects with HIV (n 39) were male (61.5%) and female (38.5%), with a mean age 37 ± 11 years. Controls (n 47) were male (36%) and female (64%), with a mean age of 26 ± 2 years. The mean BMI of the patients with HIV was 22.5 ± 4.0 k / m2. The nutritional states were: malnutrition 3 (7.7%), normal 25 (64.1%), overweight 8 (20.5%) and obesity 3 (7.7%). In 31 (79.4%) subjects no comorbidity was detected, those found were obesity 3 (7.6%), valvular heart disease 1 82.6%), alcoholism 1 (2.6%), systemic lupus erythematosus 1 (2.6%), arterial hypertension 1 (2.6%), arterial hypertension and diabetes mellitus 1 (2.6%). The laboratory parameters of patients with HIV are described in Table 1.

Table 1. Laboratory parameters of patients with HIV (n 39)

Laboratory parameters	Mean ± DE	Range
Hemoglobin (g/dL)	10,6 ± 7,2	4,5 - 15,2
Urea (mg/dL)	29,3 ± 20,9	8 - 120
Creatinine (mg/dL)	0,7 ± 0,3	0,08 - 1,7
Potassium (mEq/L)	4,1 ± 0,7	2,7 - 7,2
Magnesium (mg/dL)	2 ± 0,2	1,6 - 2,7
Calcium (mg/dL)	8,5 ± 0,8	7 - 10,3

All HIV carriers were in stage C (AIDS), who were admitted to the hospital room for opportunistic diseases. The median viral load was 38,466 (range 80 - 11,000,000 and the median CD4 count was 80 (range 22 - 644). In 11 (28%) subjects, recruitment was carried out when debuting with AIDS, while 28 (72%) were on Atripla © treatment for an average of 12 months.

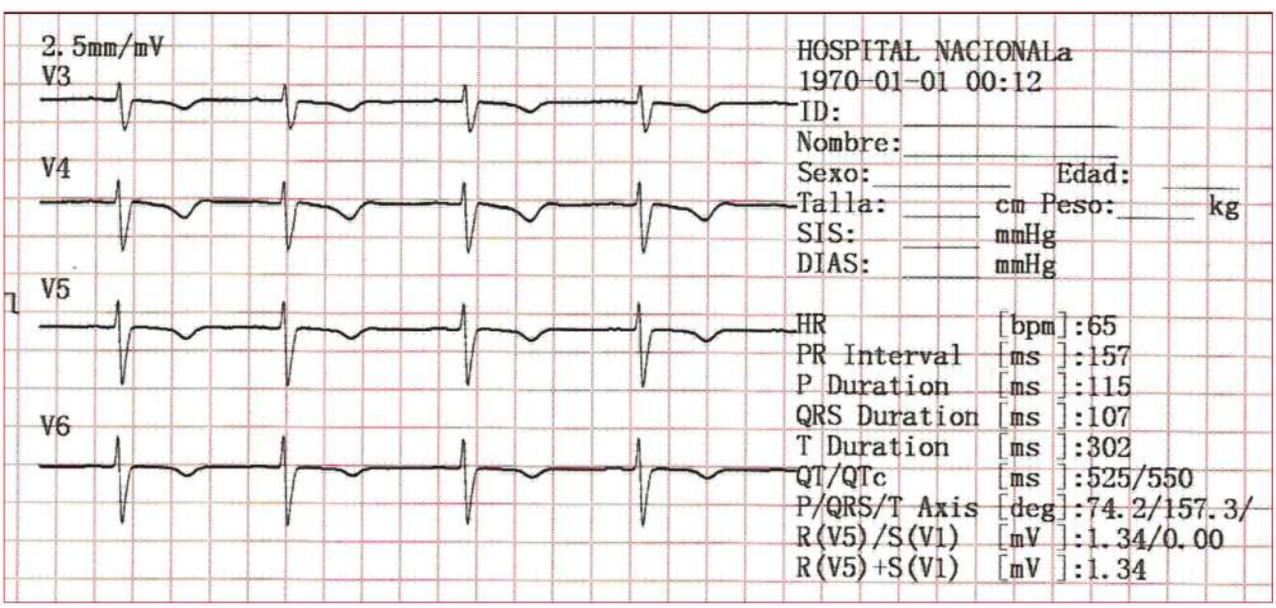
All patients were in sinus rhythm. The electrocardiographic findings are detailed in Table 2.

Table 2. Electrocardiographic findings with HIV patients and healthy controls

Electrocardiographic findings	Patients with VIH (n 39)	Controls healthy (n 47)
Rate (beats / min)	89 ± 22	78 ± 13
PR interval (msec)	0,14 ± 0,02	0,14 ± 0,02
QT interval (msec)	0,33 ± 0,05	0,33 ± 0,02
QTc interval (msec)	0,40 ± 0,05	0,37 ± 0,03

Applying a cut-off point of ≥0.45 sec in men and ≥0.47 sec in women, 7 subjects (18%) were found in the cases with HIV and in none of the healthy controls (graphic 1 and figure 1).

Figure 1. Electrocardiographic tracing of a 28-year-old woman treated with antiretrovirals 2 years ago, omeprazole and carbamazepine. QTc of 0.55 msec is observed.



The 7 cases with prolonged QTc were characterized by all being on antiretroviral treatment. There was no significant variation in the other clinical and laboratory parameters (Table 3).

Table 3. Clinical and laboratory characteristics of patients with HIV in relation to the QTc interval (n 39)

Clinical characteristics	With QTc prolonged (n 7)	With QTc normal (n 32)
Sex female/male	3/4	12/20
Edad (mean ± SD)	39 ± 10	37 ± 11
BMI (mean ± SD)	21 ± 5	23 ± 4
Urea (mean ± SD)	37 ± 29	27 ± 19
Creatinine (mean ± SD)	0,9 ± 0,4	0,7 ± 0,1
Potassium (mean ± SD)	3,6 ± 0,6	4,2 ± 0,7
Magnesium (mean ± SD)	2 ± 0,3	2 ± 0,2
Calcium (mean ± SD)	8,8 ± 0,6	8,5 ± 0,8
With antiretrovirals (n 28)	7 (100%)	21 (65%)

All patients with HIV were polypharmacy. The medications most used by the 7 patients with prolonged QTc and their relationship with the risk of developing arrhythmias according to AZCERT are described in Table 4.

Discussion

National SQTP data in Medical Clinic patients report a frequency of 21% but included few AIDS patients

Table 4. Frequency of drugs ingested by patients with prolonged QTc classified according to the risk of developing arrhythmias (n 7)

Known Risk	Possible Risk	Conditioned Risk	Prohibited in congenital long QT
azithromycin (71%)	efavirenz (100%)	omeprazol (100%)	cotrimoxazole (57%)
fluconazole (57%)		amphotericin B (14%)	
ondansetron (28%)			

(19). In this study, the frequency of PCOS was very high (18%), even more so when compared with healthy controls, which shows the clear association between HIV, antiretroviral drugs and QT interval alteration.

According to various authors, the frequency of PCOS in HIV-infected patients varies between 1.1 and 45% (13,14,20,21). In studies where control groups were used, the frequency of PTSD was higher in patients with HIV: 34% vs. 10.5% (22), 22.8% vs. 3.9% (15), 11% vs. 9%, 29% vs. 7%, 32% vs. 4.7%, 48% vs. 8%. This demonstrates the clear association between this disorder on the ECG and HIV infection, although the etiology of this abnormality is multifactorial (23).

The QTc interval is an electrical activity mediated by channels that regulate ionic fluxes through it. The rapid entry of positive Na and Ca ions through these channels is responsible for normal myocardial depolarization, while repolarization occurs when this flow is exceeded by the exit of K ions (24). The dysfunction of these channels or channelopathy generates an intracellular excess of cations (Na and K), either due to insufficient K output or excessive Na input, which delays ventricular repolarization and the QT interval is prolonged (2). In this sample, no abnormalities in electrolyte concentrations were detected to explain the SQTP.

Increased duration of the QT interval on the ECG has been associated with an increased risk of severe arrhythmias and sudden death, as it favors the development of the potentially fatal "tip torsion" helical ventricular tachycardia. Arrhythmias can manifest as palpitations, syncope, cardiogenic shock, or sudden death (7). Sudden death is understood to be that which occurs within 1 h in a person with no previous signs of fatality. The autopsy does not show organic signs of myocardial damage, since one cause could be arrhythmogenic channelopathies, especially in those under 40 years of age (4). Fortunately, no in-hospital death occurred in this sample.

Alterations in the ECG of AIDS patients can occur in all waves and segments (25) (26). Soliman et al. found these alterations in 51% while in the general population it was only in 16 to 32% (13). These ECG abnormalities were associated with greater cardiovascular complications, especially in subjects with comorbidities such as dyslipidemia, arterial hypertension, diabetes mellitus, and smoking. Autonomic neuropathy increases the frequency of PCOS to 65% (21) (26). In this study, the patients with HIV did not present mainly comorbidities, so the PQTS cannot be attributed to them.

In this sample, all the subjects with PCOS were on antiretroviral treatment and also received medications registered on the AZCERT list, due to their known association with this electrocardiographic alteration (10). Unfortunately, there are no ECG records at the start of treatment or follow-up at discharge.

Antiretroviral treatment in Paraguay includes efavirenz / emtricitabine / tenofovir disoproxil. The former is a non-nucleoside reverse transcriptase inhibitor (NNRTI) while the others are nucleoside reverse transcriptase inhibitor (NNRTI) (16). Except for efavirenz, this formulation has mostly renal excretion (27). Many antiretrovirals are associated with SQTP. The concomitant use of macrolides, cotrimoxazole, antivirals and antifungals, very common in AIDS, increases the risk of QTc interval prolongation (14,15). The risk of sudden death in patients with HIV is 4.5 times more frequent than in subjects without this infection (5). This risk is due not only to PCOS but also to the increase in coronary risk factors due to chronic inflammation, dyslipidemia, endothelial and platelet dysfunction, generating ischemic heart disease and heart failure (27).

A weakness of this research is the small sample size. This was due to the fact that outpatients could not be recruited due to the contact restriction established by the health protocol as a result of the SARS-CoV-2 pandemic (28). For this reason, only the internees were included. Another weakness is the cross-sectional design that prevents determining the association between variables and evolutionary monitoring. Nor can it be conclusively concluded that only antiretrovirals were the cause of PTSD due to polypharmacy, which is difficult to avoid in these complex patients. But as a strength, it should be mentioned that it is the first study to address this issue in patients with HIV in this referral hospital, an aspect that must be taken into account in their follow-up. For this reason, ECG is recommended when starting and during antiretroviral treatment (29,30).

In conclusion, the frequency of SQTP in HIV patients was 18% and 0% in healthy controls. All these patients with electrocardiographic alteration

were on antiretroviral treatment and received drugs recognized for generating this electrocardiographic abnormality. Periodic ECG monitoring is recommended in HIV patients receiving drugs that prolong the QT interval, as well as methodological designs that assess risk.

Funding

This research was funding by the School of Medicine to the Private University of the East, Asuncion, Paraguay.

Authors' contributions

All authors participated in the entire research process.

Conflict of interests

The authors report having no conflicts of interest.

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