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Research Article

Behavior of QT Interval in HIV-Infected Patients Receiving Antiretroviral Therapy

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Abstract

Background: Human immunodeficiency virus infections have been associated with arrhythmias, in which antiretroviral drugs play a major etiological role.

Objective: To describe the behavior of the QT interval and its dispersion among patients with positive human immunodeficiency virus under antiretroviral treatment.

Methods: A descriptive, longitudinal and prospective study was carried out in 1139 patients with human immunodeficiency virus. The demographic variables (sex, age), epidemiological (cardiovascular risk factors), immunological (viral load, CD4+ count) and electrocardiographic variables (corrected QT, QT dispersion, ventricular arrhythmias) were analyzed.

Results: Male sex, tobacco and opportunistic infections were the most prevalent. The immunological variables responded adequately to the antiretroviral. There was a nonpathological increase in QT interval and QT dispersion, especially when lopinavir was used. Ventricular arrhythmias were reported in 23.6% and sudden death in 10%.

Conclusions: Prolongation and dispersion of the QT interval, ventricular arrhythmias and sudden death were associated with HIV infection that was short-lived and associated with protease inhibitors.

Keywords: *Antiretroviral; AIDS/HIV; Malignant Arrhythmias; QT Prolongation; QT Dispersion; Sudden Death*

Abbreviations

AIDS/HIV: Acquired Immunodeficiency Syndrome/Human Immunodeficiency Virus; QT: Interval QT; Δ QT: Dispersion of QT Interval; ms: Millisecond

Introduction

Between the infections with bigger morbidity and mortality of the modern world finds the acquired immunodeficiency syndrome (AIDS). The United Nations declared to the infection by the human immunodeficiency virus (HIV) as a situation of worldwide emergency with devastating consequences, in 2017, 36.9 million (31.1 million - 43.9 million) people globally were living with HIV [1].

Cuba not it finds foreign to the international reality, if it show attainments as the fact that on 30th July of the 2015, Cuba was converted in the first country of the world in receiving the validity of the World Health Organization of having eliminated the transmission from mother to child of HIV and the syphilis [2]. HIV and AIDS estimates of adults and children living with HIV in 2017 in Cuba was 30 000 (26 000 - 33 000) [3].

HIV infection and AIDS are known to affect the heart and produce disease. Cardiac manifestations of HIV and AIDS have become increasingly important causes of morbidity and mortality [4-6]. With the development of antiretroviral therapy, the mortality rate from infection has decreased significantly in HIV-infected patients [4-8], but this treatment also has systemic repercussions in the cardiovascular system like coronary ischemia, systolic dysfunction, arrhythmias and sudden death [4-6]. The antiretroviral therapy lengthens the QT interval and has risk for Torsade de pointes and sudden death [8,9].

Objective of the Study

The objective of this study was to describe the behavior of the QT interval and its dispersion among patients with positive HIV under antiretroviral treatment.

Materials and Methods

A descriptive, longitudinal, prospective study was carried out to characterize the electrocardiographic pattern of the Qtc interval and its dispersion of patients with AIDS.

Population studied

The Scientific Committee of the institution approved the study protocol and informed consent was obtained from all subjects enrolled in this study.

Between February 2006 and February 2016, 1139 HIV-infected patients (aged > 18 years) attending the institution were enrolled. These patients without a cardiovascular history, or QT interval alterations, initiate early different protocols of highly effective antiretroviral treatments.

Clinical evaluation

The clinical evaluation (blood analysis and 12-lead electrocardiogram) was repeated at three different times in time (at the time of diagnosis, five and ten years of treatment). In addition, he performed a 24-hour Holter registry at 5 and 10 years of follow-up.

For the measurement of the QT interval, the advantage and the technique of the tangent, the value corrected as a function of the RR interval was calculated using the formula Bazzet ($QTcB = QT/\sqrt{RR}$) and Fridericia ($QTcF = QT/3\sqrt{RR}$).

The dispersion of the QT interval between the greater and the uncorrected smaller QT interval of the precordial leads of the same 12-lead electrocardiogram. Long QT is considered when the QTcB in the DII lead ≥ 460 ms in women and ≥ 450 ms in men.

The presence of malignant arrhythmias used in the 24-hour electrocardiographic study (Holter) was documented.

Statistical analysis

It was used the percentage in the categorical and continuous variables. Means and standard deviations of means expressed the results. Student's t- test for continuous variables and chi-squared test for categorical variables evaluated the statistical significance for paired samples, previously checked that the data complied with the premise of normality.

To value the report between the alterations of the QT interval and its dispersion, according to the treatment with antiretrovirals, with regard to the risk of arrhythmias carried out a bivariate analysis by comparing the presence in function of pharmacological groups, as well as an analysis with the method of logistic regression between electrocardiographic variables associated to arrhythmias.

Differences were considered statistically significant for $p < 0.05$ with CI of 95%. Statistical software package SPSS version 17.0 (Chicago, IL, USA) was used for analysis.

Results and Discussion

One-hundred thousand thirty and nine cases were studied: 115 females and 1024 males (Table 1). The AIDS patients were aged between 18 - 76 years. It had an evident prevalence of the masculine sex (98.5%) with a mean age's ± standard deviation (SD) of 37.9 ± 8.85 years.

Variables	Female		Male		p
	n = 115		n = 1024		(*p < 0.005)
Age	Total	%	Total	%	
18 - 27	21	18.2	144	14.6	0.4
28 - 37	47	40.8	303	29.5	0.03*
38 - 47	27	23.4	248	24.2	0.5
48 - 57	19	16.5	190	18.5	0.8
58 - 67	1	0.86	29	2.83	0.2
68 - 76	0	0	18	1.75	0.1
76+	0	0	2	0.19	0.1
Mean ± SD	31.8 ± 9.2		37.9 ± 8.5		

Table 1: *Demographical characteristic of patients with AIDS/HIV.*

Between the epidemiological variables that they throve were the habit of smoking (70.4%) and the opportunistic infections (19.5%), where predominated cytomegalovirus (21%).

Table 2 documents the relationship between immunological biomarker in three points of cut of the study: diagnostic, five and ten years, with an increment of T cells CD4+ as being established the different antiretroviral treatments, and in correspondence it documented a progressive reduction of the viral load to the five and ten years as effective response to the treatment. The changes referred to the count of T cells CD4+ as well as for the viral load were statistically significative.

Table 3 shows the QTc calculated by Bazett and Fridericia formulas in the three moments of the study for the different treatments: protease inhibitors such as: saquinavir (SQV/r), lopinavir (LPV/r), atazanavir (ATZ/r) and others protease inhibitors (PI), nucleoside analog reverse transcriptase inhibitors (NARTI), and non-nucleoside analog reverse transcriptase inhibitors (nNARTI). The QTc had a temporal tendency towards the progressive increment, although not exceeded the superior threshold value of the normality. The three protease inhibitors: saquinavir (SQV/r), lopinavir (LPV/r), atazanavir (ATZ/r) showed a tendency of lengthen the QTc interval and the QT dispersion, although without becoming pathological they was increased progressively in time. In de multivariate analysis of the relationship between antiretrovirals responsible of the prolongation and dispersion of QT interval, these three protease inhibitors marked the protagonism of these results, so much of the prolongation as for the dispersion of the QT interval, although without becoming pathological it is increased progressively in time (Table 4).

Variables	Diagnostic Mean ± SD		5 years Mean ± SD		10 years Mean ± SD		p
T CD4+	148 ± 29.1		364 ± 68.5		538 ± 70.6		0.03*
Viral load	250000 ± 56.9		87000 ± 70.3		43000 ± 93.4		0.003*
Antiretroviral	T	%	T	%	T	%	
First line: 306 (26.8%)							
Nevirapine (200 mg) (nNARTI) Lamivudine (200 mg) (NARTI)	172	56.2	77	25.1	57	18.6	0.03*
Tenofivir (NARTI) Lamivudine (NARTI)	35	4.24	43	5.21	59	7.16	0.4
Efavirenz (nNARTI) Zidovudine (NARTI)	32	3.88	35	4.24	36	4.36	0.2
Tripanavir (PI) Abacavir (NARTI) (300 mg)	20	2.42	0	0	0	0	0.3
KALETRA: Lopinavir 200 mg + Ritonavir 50 mg (PI)	34	4.12	37	4.49	40	4.85	0.2
Second line: 824 (72.3%)							
TRUVADA: Tenofovir (300 mg) (NARTI) + Entricitabine (NARTI)	32	3.88	41	4.97	52	6.31	0.4
Saquinavir (500 mg) (PI) + Ritonavir (100 mg) (PI)	32	3.88	35	4.24	52	6.31	0.4
TRIPLA: Tenofivir (300 mg) (NARTI) + Emtricitavine (200 mg) + Efavirenz (600 mg) (nNARTI)	27	3.27	37	4.49	38	4.61	0.3
Third line: 9 (0.79%)							
Darunavir (PI) + Raltegravir + Ritonavir (PI)	0	0	9	0.79	9	0.79	0.2

Table 2: *Relationship between immunological biomarker and antiretroviral treatment in patients with AIDS/HIV.*

NARTI: Nucleoside Analog Reverse Transcriptase Inhibitor; nNARTI: Non-Nucleoside Analog Reverse Transcriptase Inhibitors; PI: Protease Inhibitors.

			Protease Inhibitors				
Variables		**Patients**	**SQV/r**	**LPV/r**	**ATV/r**	**Others PI**	**NARTI-nNARTI**
Time of the study	Bazett: n%	1139 (100%)	119 (10.4%)	111 (9.74%)	107 (9.39%)	29 (2.54%)	773 (67.8%)
	QTcB (mean ± SD)	415.6 ± 18.6	421 ± 19.3	412.7 ± 16.6	413.6 ± 16.6	414.7±18.6	405.8 ± 20.0
Diagnostic	QTcB M	1024(89.9%)	367 ± 23.5	356 ± 23.6	362 ± 23.5	357 ± 23.4	355 ± 23.4
	QTcB F	115 (10.0%)	387 ± 21.3	378 ± 22.7	371 ± 23.6	368 ± 23.1	359 ± 23.0
5 years	QTcB M	1024(89.9%)	434 ± 22.3	436 ± 22.8	430 ± 22.7	440 ± 22.3	368 ± 22.0
	QTcB F	115 (10.0%)	457 ± 21.8	467 ± 21.8	459 ± 22.5	447 ± 22.0	389 ± 22.8
10 years	QTcB M	1024 (89.9%)	447 ± 15.4	443 ± 16.7	439 ± 17.8	440 ± 18.5	369 ± 17.0
	QTcB F	115 (10.0%)	454 ± 17.6	456 ± 17.8	456 ± 16.8	455 ± 17.0	399 ± 18.9
Diagnostic	Δ QT	1024 (89.9%)	56 ± 18.9	56 ± 17.0	54 ±16.9	53 ± 17.3	54 ± 16.0
5 years	Δ QT	1024 (89.9%)	58 ± 16.8	58 ± 17.5	55 ± 18.0	56 ± 16.9	55 ± 18.3
10 years	Δ QT	1024 (89.9%)	68.9 ± 15.5	66.5 ± 16.0	67.4 ± 15.9	68.2 ± 15.4	58.7 ± 16.7
Time of the study	Friderician (%)	1139(100%)	119(10.4%)	111 (9.74%)	107 (9.39%)	29 (2.54%)	773 (67.8%)
	QTcF (mean ± SD)	406.2 ± 18.3	Z412.2 ±18.1	404.8 ± 16.6	405.5 ± 17.4	406.2±18.7	403.4 ± 20.0

Diagnostic	QTcF M	1024 (89.9%)	366 ± 23.2	355 ± 22.6	361 ± 23.4	363 ± 23.2	353 ± 23.4
	QTcF F	115 (10.0%)	384 ± 21.0	377 ± 22.6	370 ± 23.5	366 ± 23.0	357 ± 23.0
5 years	QTcF M	1024(89.9%)	432 ± 22.4	435 ± 22.7	429 ± 22.6	440 ± 22.1	367 ± 22.0
	QTcF F	115 (10.0%)	455 ± 21.6	466 ± 21.7	458 ± 22.4	445 ± 22.0	378 ± 22.8
10 years	QTcF M	1024(89.9%)	445 ± 15.2	442 ±16.6	438 ± 17.7	440 ± 18.2	387 ±17.0
	QTcF F	115 (10.0%)	452 ± 17.4	450 ± 17.7	455 ± 16.7	456 ± 17.0	397 ± 18.9
Diagnostic	Δ QT	1024(89.9%)	53 ± 18.6	55 ± 16.0	54 ± 16.8	54 ± 17.2	55 ± 16.0
5 years	Δ QT	1024(89.9%)	55 ± 16.6	57 ± 17.4	59 ± 17.0	55 ± 16.6	56 ± 18.3
10 years	Δ QT	1024(89.9%)	64.6 ± 15.3	65.5 ± 16.0	62.3 ± 15.8	63.1 ± 15.2	62.1 ± 16.7

Table 3: *QTc and dispersion of QT interval with different antiretroviral treatments in the three moments of evolution in patients with AIDS/HIV.*

NARTI: Nucleoside Analog Reverse Transcriptase Inhibitor; nNARTI: Non-Nucleoside Analog Reverse Transcriptase Inhibitors; PI: protease inhibitors. Saquinavir (SQV/r), Lopinavir (LPV/r), Atazanavir (ATZ/r).

Variables	n	Diagnostic (mean ± SD)	5 years (mean ± SD)	10 years (mean ± SD)	OR (CI 95%)	p
QTcB (mean ± SD)						
LPV/r	111 (9.74%)	366 ± 23.1	451 ± 22.2	447 ± 17.2	1.50 (0.62-1.24)	0.10
SQV/r	119 (10.4%)	376 ± 22.2	444 ± 22.1	449 ± 16.4	0.43 (0.59-1.93)	0.02
ATV/r	107 (9.39%)	366 ± 23.5	444 ± 22.5	447 ± 17.2	0.32 (0.67-1.44)	0.01
Others PI	29 (2.54%)	363 ± 23.1	443 ± 22.1	447 ± 17.6	0.98 (0.56-0.68)	0.03
NARTI-nNARTI	773 (67.8%)	356 ± 23.2	375 ± 22.4	388 ± 17.9	0.44 (0.67-1.45)	0.04
Δ QT (mean ± SD)						
Any treatment	58.4 ± 16.7	54.4 ± 17.0	56.4 ± 17.3	64.7 ± 15.8	0.38 (0.54-1.34)	0.01
LPV/r	59.6 ± 16.6	55.5 ± 16.5	57.5 ± 17.4	66.0 ± 16.0	1.50 (0.52-1.04)	0.01
SQV/r	59.2 ± 16.9	54.5 ± 18.7	56.5 ± 16.7	66.7 ± 15.4	0.39 (0.64-1.93)	0.02
ATV/r	58.6 ± 16.7	54.0 ± 16.8	57.0 ± 17.5	64.8 ± 15.8	0.59 (0.56-0.68)	0.02
Others PI	58.2 ± 16.4	53.5 ± 17.2	55.5 ± 16.7	65.6 ± 15.3	0.37 (0.45-1.54)	0.01
NARTI-nNARTI	56.8 ± 17.0	54.5 ± 16.0	55.5 ± 18.3	60.4 ± 16.7	0.47 (0.80-0.53)	0.01

Table 4: *Analysis of behavior of QTc and dispersion of QT interval (Δ QT) with different treatments with antiretrovirals in patients with HIV/AIDS.*

NARTI: Nucleoside Analog Reverse Transcriptase Inhibitor; nNARTI: Non-Nucleoside Analog Reverse Transcriptase Inhibitors; PI: protease inhibitors. Saquinavir (SQV/r), Lopinavir (LPV/r), Atazanavir (ATZ/r).

It documented 269 (23.6%) malignant arrhythmias and 115 (10.0%) cases of sudden death in relation with the antiretroviral used treatment. It had a significant increment (p = 0.002) in the occurrence of arrhythmias as of the 5 and 10 years of the evolution of study in the treatment with protease inhibitors. To the diagnostic it had a report of 20 cases of arrhythmias and sudden deaths with the use of atazanavir (ATZ/r), while that it had any report of these events with the use of Nucleoside analog reverse transcriptase inhibitors (NARTI) or with non-nucleoside analog reverse transcriptase inhibitors (nNARTI) (See table 5).

	Protease Inhibitors						
Variables	**SQV/r**	**LPV/r**	**ATZ/r**	**Others PI**	**NARTI-nNARTI**	**OR (CI 95%)**	**p**
n	119 (10.4%)	111 (9.74%)	107 (9.39%)	29 (2.54%)	773 (67.8%)		
Arrhythmias							
Diagnostic	0	0	20 (18.6%)	0	0	0.97 (0.941.00)	0.27
5 years	31 (26.0%)	44 (39.6%)	0	11 (37.9%)	0	1.50 (0.723.14)	0.05
10 years	66 (55.4%)	80 (72.0%)	0	17 (58.6%)	0	2.33 (1.516.88)	0.002*
Sudden Death							
Diagnostic	0	0	20	0	0	0.32 (0.071.44)	0.27
5 years	15 (12.6%)	12 (10.8%)	0	4 (13.7%)	0	1.50 (0.723.14)	0.14
10 years	23 (19.3%)	33 (29.7%)	0	8 (27.5%)	0	1.32 (0.781.34)	0.01

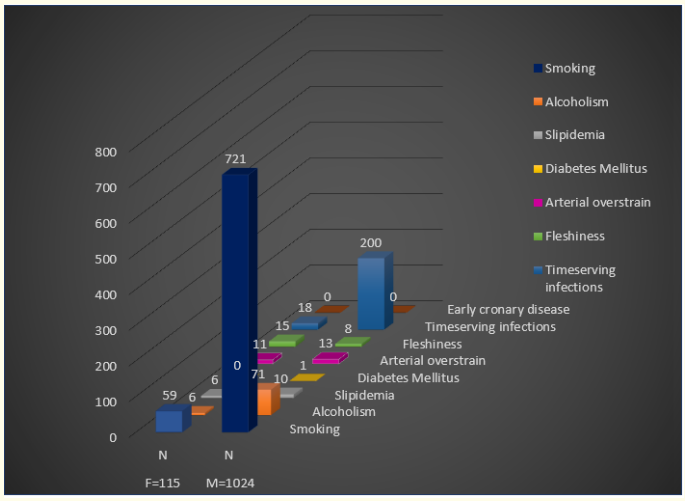
Table 5: *Multivariate analysis between arrhythmias, sudden death and antiretroviral treatment in patients with HIV/AIDS.*

Table 6 shows the documented arrhythmias. Along the evolution of patients, it appreciated an increment in the occurrence of arrhythmias. Notwithstanding this not occurs for the ventricular sustained tachycardias that show a falling tendency along time (Table 6). It is interesting to point out that the Torsade de Pointes (TdP) surpasses in prevalence to the other categories of arrhythmic events.

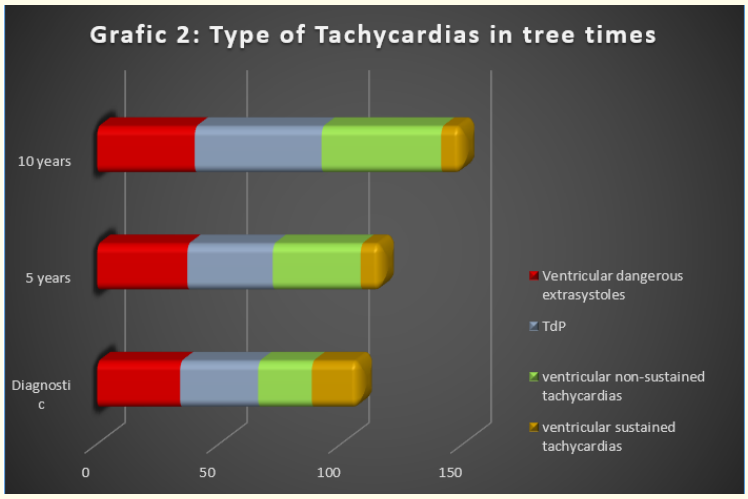
	Diagnostic	5 years	10 years
Type of arrythmia			
Ventricular dangerous extrasystoles	34	37	40
TdP	32	35	52
ventricular non-sustained tachycardias	22	36	49
ventricular sustained tachycardias	20	9	9

Table 6: *Documented arrhythmias in patients with HIV/AIDS.*

TdP: Torsades of Pointes



Graph 1: *Epidemiologic variables in AIDS/sida patients, for sex. 2006-2016 (n = 1139).*



Graph 2: *Type of Tachycardias in tree times.*

Discussion

This study aimed to assess the extent to which exposure to antiretroviral therapy in patients with AIDS/HIV is associated with lengthening or dispersion in the QT interval.

The cardiovascular illness between the patients with AIDS/HIV is more frequent than in the general population of the same age and sex, with a prevalence that has gone in increase according to studies of cohort [4,8,10]. The base of this bigger cardiovascular risk appears is multifactorial. For a side it has made evident a bigger incidence of the classic cardiovascular risk factor in this group of patients (dyslipidemia, tobacco, hypertension and hyperglycemia) [11]. Moreover, the own infection for HIV has weight a state inflammatory chronic proaterogenic associated to the own virus and to the prolonged exposition to the antiretroviral treatment [12]. For this motive some authors already identify to the HIV as a risk of factor per se [4,13].

Between the cardiovascular risk factor more prevalent in this study it documented the tobaccoism, which is in harmony with other studies that point out a prevalence of smoking in peoples with HIV [14,15]. In agreement with the American Heart Association the tobaccoism is the bigger amendable risk of factor that contributes to the premature morbidity and mortality of cardiovascular cause [15].

In clinical record of the affected patients of this study, it gathered that 218 (19.1%) of them presented infection opportunists, it who for effects of this work has particular transcendence because the conducting therapeutics in front of this infections involves the use of drugs that can increase the adverse cardiovascular effects of the antiretroviral treatment. The cytomegalovirus infection was the most frequent of the infection opportunists founded in the patients of the study; this microorganism is considered common between patients with AIDS/HIV. Is difficult to relate the individual action of the cytomegalovirus to the evolution of the infection in patients with AIDS/HIV [16].

In this work, the immunological variables (viral load and count of T cells CD4+) in patients with AIDS/HIV show a significative tendency to the improvement with the antiretroviral treatment. These results are in according with others groups as AIDS Cohort Study (MACS) [17], the Understand the Natural History of AIDS/HIV in the Era of Effective Therapy (SUN) [18] and the French Hospital Database on HIV (FHDH)-ANRS CO4 [19], all they report that the antiretroviral treatment not only reduces the viral load but that also improvement the cardiovascular events.

In this study saquinavir (SQV/r), lopinavir (LPV/r) and atazanavir (ATZ/r) showed a tendency of lengthen the QTc interval and the QT dispersion. These actions were reported before [9,20-24]. Archacho., *et al*. (2010) [25], showed that the prolonged use of atazanavir can prolong the QT interval but rarely to values above the superior limit of the normality for each sex, like the present results. Not found statistical significant superiority between the values of QT obtained in patients with saquinavir (SQV/r) treatment in comparison with others protease inhibitors (PI) or with antiretrovirals of other groups, unlike with report of Thienemann., *et al*. (2013) [24]. On the contrary in the present results it founded that the Odds Ratio for the prolongation of QT is bigger in the group of patients treated with lopinavir (LPV/r).

Soliman., *et al*. (2011) [23] published risk factor for the prolongation of QT interval in patients with HIV according to the use of Bazzet formula or Fridericia, in this results not found significant differences between the values obtained by theses formulas, it is probably to that cardiac frequency of the studied patients was in the interval of 60 to 100 beats per minute, range for which diverse studies consider that the selected formula does not bear upon the obtained results [26].

As for the dispersion of the QT interval in this study, the tendency was a lineal increment with respect to the time of evolution without significative differences to the used treatment. Other authors find superior values of dispersion of the QT interval in the groups of patients treated with PI [27]. The explanation of this phenomenon can be by the possible interaction of predisposing factors for prolongation of QT interval and torsadogenic, those which were tried to avoid in the patients of this study, especially in the adjustment of the dose of the antiretrovirals, selections of additional drugs, and in the proper maintenance of the internal environment. In the present results the only group of patients that showed a tendency to increase the dispersion of QT interval was the group of patient treated with lopinavir (OR = 1.50 (IC 0.52 - 1.04)).

The Food and Drug Administration has broadcasted warnings on the potential proarrhythmic of PI, particularly of lopinavir [28], by emphasizing in its capacitance of prolonging the QT interval and predispose to TdP. This coincides with the results of this study as for the find of bigger measurements of the QT interval in patients with treatment of lopinavir.

Charbit., *et al*. (2008) [29], showed a prolongation of QT interval in patients with AIDS/HIV associated with risk factors as incomplete bundle branch block, ventricular hypertrophy, signs of ischaemic cardiopathy, female gender, White ethnic origin, age and, the duration of HIV infection, but the QT lengthening was not associated with the treatment of any antiretroviral drug. In the SMART randomized trial [23], concluded that the protocols of treatment with PI have a minimum effect on QT compared with the protocols based on nNARTI.

As for the results with report to adverse arrthymic events it is of pointing out that the sudden death in 20 patients treated with atazanavir at the beginning of the study, apparently is a drug-independent factor, apparently they existed of some comorboses factors that they conduct to these complications. Specific studies with atazanavir stand out its below cardiovascular risk [30], in spite of it blocks directly the hERG K+ channel [31].

It was in this study an increment in TdP in the follow-up of patients, like the ventricular non-sustained tachycardia's. In an interesting way it had a falling tendency for the ventricular sustained tachycardia's, it could be related with a bigger degree of electric instability in the more advances stages of HIV infection, but this hypothesis requires of later analysis that asses it in a specific way.

Conclusion

The duration of HIV infection is corresponded with an evolution of lengthening in the QT interval and its dispersion, without becoming pathological. The prolongation of QT is bigger in the group of patients treated with lopinavir. Ventricular arrhythmias and sudden death were related to HIV infection lasting and poorly associated to protease inhibitors and any other antiretroviral.

This study is an approach to the problem of the proarrthymias in the HIV infection context. Further researches of major magnitude, with bigger inclusion of patients and perspectives are needed to confirm these findings.

Conflict of Interest

We have no conflict of interest.

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