ElectroCardioGraphic QTc Interval Prolongation in Aging THAI HIV infected Population After Receiving AntiRetroviral Therapy: ECG THAI-HAART Study

Mr. Nonthikorn Theerasuwipakorn

A Thesis Submitted in Partial Fulfillment of the Requirements

for the Degree of Master of Science in Medicine

Department of Medicine

FACULTY OF MEDICINE

Chulalongkorn University

Academic Year 2019

ภาวะการนำไฟฟ้าหัวใจผิดปกติชนิดคิวทียาว ในผู้ป่วยติดเชื้อเอชไอวีสูงอายุที่ได้รับยาต้านเชื้อไวรัส

นายนนทิกร ธีรสุวิภากร

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาอายุรศาสตร์ ภาควิชาอายุรศาสตร์
คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2562

Thesis Title	ElectroCardioGraphic QTc Interval Prolongation in Aging THAI HIV infected Population After Receiving AntiRetroviral Therapy: ECG THAI-HAART Study
By	Mr. Nonthikorn Theerasuwipakorn
Field of Study	Medicine
Thesis Advisor	Assistant Professor Pairoj Chattranukulchai, M.D.
Thesis Co Advisor	Voravut Rungpradubvong, M.D.
	Anchalee Avihingsanon, M.D.

Accepted by the FACULTY OF MEDICINE, Chulalongkorn University in Partial Fulfillment of the Requirement for the Master of Science

..... Dean of the FACULTY OF MEDICINE
(Professor SUTTIPONG WACHARASINDHU, M.D.)

THESIS COMMITTEE

..... Chairman
(Associate Professor HIROSHI CHANTAPHAKUL, M.D.)

..... Thesis Advisor
(Assistant Professor Pairoj Chattranukulchai, M.D.)

..... Thesis Co-Advisor
(Voravut Rungpradubvong, M.D.)

..... Thesis Co-Advisor
(Anchalee Avihingsanon, M.D.)

..... Examiner
(WORAWAN SIRICHANA, M.D.)

..... External Examiner
(Assistant Professor Pattarapong Makarawate, M.D.)

นนทิกร ธีรสุวิภากร : ภาวะการนำไฟฟ้าหัวใจผิดปกติชนิดคิวทียาว ในผู้ป่วยติดเชื้อเอชไอวีสูงอายุที่ได้รับยาต้านเชื้อไวรัส. (ElectroCardioGraphic QTc Interval Prolongation in Aging THAI HIV infected Population After Receiving AntiRetroviral Therapy: ECG THAI-HAART Study) อ.ที่ปรึกษาหลัก : ผศ. นพ.ไพโรจน์ ฉัตรานุกูลชัย, อ.ที่ปรึกษาร่วม : อ. นพ.วรวุฒิ รุ่งประดับวงศ์,อ. พญ.อัญชลี อวิหิงสานนท์

บทนำ: ภาวะ QTc interval prolongation เป็นภาวะที่พบได้บ่อยในผู้ป่วยติดเชื้อเอชไอวี ข้อมูลจากงานวิจัยในอดีตยังเป็นที่ถกเถียงกันว่า ยาต้านเชื้อไวรัสมีความสัมพันธ์กับการเกิดภาวะดังกล่าวหรือไม่ นอกจากนี้ในปัจจุบันมียาต้านชนิดใหม่ออกมามากขึ้น ซึ่งยังมีข้อมูลน้อย และยังไม่มีการศึกษาใดที่ศึกษาในผู้ป่วยสูงอายุ

ระเบียบวิธีการทำวิจัย: การศึกษานี้เป็นการเก็บรวบรวมข้อมูลในผู้ป่วยติดเชื้อ และรับประทานยาต้านเชื้อเอชไอวี อายุ 50 ปีขึ้นไป และเคยได้รับการบันทึกคลื่นไฟฟ้าหัวใจด้วยระบบข้อมูลคอมพิวเตอร์ ในศูนย์ประสานความร่วมมือระหว่างไทย-ออสเตรเลีย-เนเธอร์แลนด์ เพื่อการวิจัยทางคลินิกด้านโรคเอดส์ (HIV-NAT) เพื่อศึกษาความชุกของภาวะ QTc interval prolongation ในผู้ป่วยกลุ่มนี้เป็นวัตถุประสงค์หลัก และศึกษาเพิ่มว่าปัจจัยใด มีความสัมพันธ์กับการเกิดภาวะดังกล่าว เป็นวัตถุประสงค์รอง ด้วยการทำการศึกษาแบบ age and sex propensity score matched case-control study ในอัตราส่วน 1 ต่อ 2 โดยนิยามภาวะ QTc interval prolongation ว่า QTc interval มากกว่า 450 ms ในผู้ชาย และ QTc interval มากกว่า 460 ms ในผู้หญิง

ผลการศึกษา: จากการรวบรวมข้อมูลตั้งแต่เดือนมกราคม 2019 ถึง เดือนพฤศจิกายน 2019 มีผู้ป่วย 413 คน ที่ตรงตามเกณฑ์คัดเลือก อายุเฉลี่ยของผู้ป่วยเท่ากับ 56.0 (50-76) ปี มีผู้ป่วยเพศชาย 249 (60.3%) คน ไม่พบผู้ป่วยที่มีภาวะเอดส์ และผู้ป่วยเกือบทั้งหมดมีโรคอยู่ในระยะความคุม ระดับเม็ดเลือดขาว CD4 เท่ากับ 640.46 +/- 242.98 cells/mcl และผู้ป่วย 401 (97.1%) ตรวจไม่พบเชื้อไวรัสในกระแสเลือด จากการวิเคราะห์พบว่าอายุที่มากขึ้น โรคความดันโลหิตสูง และการใช้ยา Nevirapine สัมพันธ์กับภาวะ QTc interval prolongation ในการวิเคราะห์แบบ unmatched case-control study แต่ไม่พบความสัมพันธ์ดังกล่าวหลังจาก matched นอกจากนี้ในการวิเคราะห์แบบ univariable analysis ยังพบว่าการใช้ยา Tenofovir alafenamide และ Atazanavir สัมพันธ์กับภาวะดังกล่าว แต่เมื่อได้รับการปรับปัจจัยกวนด้วย multivariable analysis กลับพบว่าไม่มีปัจจัยใดเลยที่มีความสัมพันธ์

สรุป: ความชุกของภาวะ QTc interval prolongation ในผู้ป่วยติดเชื้อเอชไอวีพบมากขึ้นตามอายุ และนอกจากอายุที่มากขึ้น ก็ไม่พบว่ามีปัจจัยอื่นๆที่สัมพันธ์กับภาวะดังกล่าว

สาขาวิชา	อายุรศาสตร์	ลายมือชื่อนิสิต .....
ปีการศึกษา	2562	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....
		ลายมือชื่อ อ.ที่ปรึกษาร่วม .....
		ลายมือชื่อ อ.ที่ปรึกษาร่วม .....

6174052630 : MAJOR MEDICINE

KEYWORD: HIV infection, AIDS, HAART, Antiretroviral agent, Aging, Torsades de Point, QT interval, QTc interval prolongation, PR interval, QRS duration, Electrocardiogram

Nonthikorn Theerasuwipakorn : ElectroCardioGraphic QTc Interval Prolongation in Aging THAI HIV infected Population After Receiving AntiRetroviral Therapy: ECG THAI-HAART Study. Advisor: Asst. Prof. Pairoj Chattranukulchai, M.D. Co-advisor: Voravut Rungpradubvong, M.D., Anchalee Avihingsanon, M.D.

Background: the QTc interval prolongation is commonly found in HIV infected patients with some controversial data showed the association between ART and this condition. To date, there is no data of the QTc interval prolongation in the aging HIV infected patients with the usage of current HAART regimens.

Method: we collected the data of the aging, 50 years old or more, ART-experience HIV infected patients in the HIV Netherland Australia Thailand research collaboration (HIV-NAT) who had digital ECG recorded to find the prevalence as a primary objective. The secondary objective is to find the associating factors of the QTc interval prolongation by using case-control study with age and sex propensity score matching between the patients with and without QTc interval prolongation in 1:2 ratio. The QTc interval prolongation was defined as QTc interval > 450 ms in man and > 460 ms in woman.

Result: 413 patients with the mean age of 56.0 (50-76) years old and 249 (60.3%) male patients were included from January 2019 to November 2019. There was no patient with AIDS and most of the patients were well disease control, mean CD4 level was 640.46 +/- 242.98 cells/mcl and 401 (97.1%) patients were undetectable viral load. The prevalence of the QTc interval prolongation was 22.3% (92/413). The older age, hypertension and Nevirapine use were found to associated with QTc interval prolongation in the unmatched analysis but found no association after matching. Univariable analysis of the matched case-control found the association of Tenofovir alafenamide and Atazanavir use with the QTc interval prolongation but no factor was found to be associated in multivariable analysis.

Conclusion: the prevalence of the QTc interval prolongation was higher in aging ART-experience HIV infected patient. Except the older age, there was no other factor including ART use found to associated with the QTc interval prolongation.

Field of Study:	Medicine	Student's Signature .....
Academic Year:	2019	Advisor's Signature .....
		Co-advisor's Signature .....
		Co-advisor's Signature .....

ACKNOWLEDGEMENTS

I would like to express my deep gratitude to Assistant Professor Pairoj Chattranukulchai, doctor Voravut Rungpradubvong and doctor Anchalee Avihingsanon, my research advisors and co-adviser, for their kindly guidance and useful suggestion of this research. I would also like to grateful thank Assistant Professor Smonporn Boonyaratavej Songmuang, for her support of ECG recording machine and ECG interpretation application.

My grateful thanks to Miss Dollapas Punpanich for her help in doing the data analysis and extend my thanks to the nurses and staffs of the HIV-NAT research collaboration for their help in offering me the patients' data.

Nonthikorn Theerasuwipakorn

TABLE OF CONTENTS

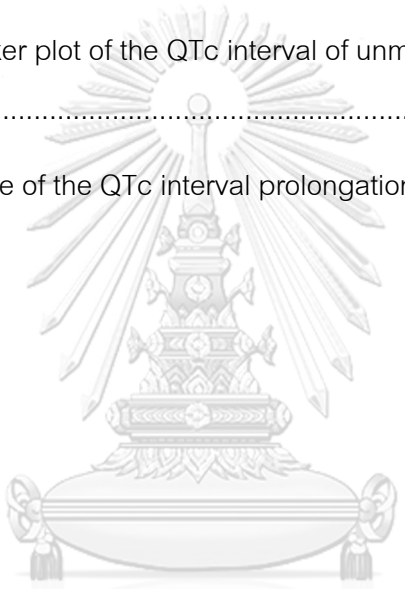
Page

LIST OF TABLES

Page

LIST OF FIGURES

Page



CHAPTER I

INTRODUCTION

1.1 Background and rationale

The QTc interval prolongation is always a preceding event of a highly morbid and mortal cardiac arrhythmia such as torsades de pointes. The QTc interval prolongation can be congenital or acquired. The commonest cause of acquired prolongation is many classes of drug which frequently use in clinical practice. The other causes, for example, are electrolyte abnormalities, structural heart diseases, bradyarrhythmia or mutations in long QT syndrome genes.

Other than the causes mentioned above, the QTc interval prolongation is commonly found in HIV infected patients; the prevalence is range from 10% to 16% depended on the population in each study. [1-3] The prevalence of QTc interval prolongation is found up to 45% in the patients with AIDs and hospitalization. [4] The probable explanation is the HIV infected patients often expose to many causes of the prolongation especially antimicrobial agents such as Macrolides, Fluoroquinolones, Co-trimoxazole, Azole antifungal agents which frequently combines and uses extensively to treating and preventing opportunistic infections. In addition, there are some evidences that HIV infection itself also increase risk of the QTc interval prolongation. [4-6]

To date, many evidences show that many risk factors of HIV infected patient including age, cardiovascular risks (hypertension, dyslipidemia, alcohol and smoking), duration of HIV infection, CD4+ level less than 200 cell/mcl and the usage of antiretroviral therapy (ART) particularly protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are causing the QTc interval prolongation. [1, 2, 7-10] Besides, there are few studies show that ART are causing PR interval and QRS duration prolongation, as well. [11-13] However, there are controversy because several studies show no association between these factors and the QTc interval prolongation.

[3, 11, 12, 14-16] Moreover, there are also the evidences that ARTs could be the protecting factor against the QTc interval prolongation. [17, 18]

Currently, the trends of HIV infection are shifted from adult to aging patients, and the treatment regimens are also change to the new era of highly active antiretroviral therapy (HAART) that consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus one of the other classes which slowly increase in the usage of newly developed agent, integrase inhibitors. Nowadays, there are no real-world studies conducted in this new HAART era to find the association between these agents and the QTc interval prolongation; in addition, there is no study that specifically conducted in the aging HIV infected patients. We need to provide more data about these issues. [19-23]

1.2 Research Questions

1.2.1 Primary Research Question

What is the prevalence of QTc interval prolongation in ART-experienced HIV infected population in the current HAART era?

1.2.2 Secondary Research Question

What are the associating factors of QTc interval prolongation in ART-experienced HIV infected population in the current HAART era?

1.3 Conceptual Framework

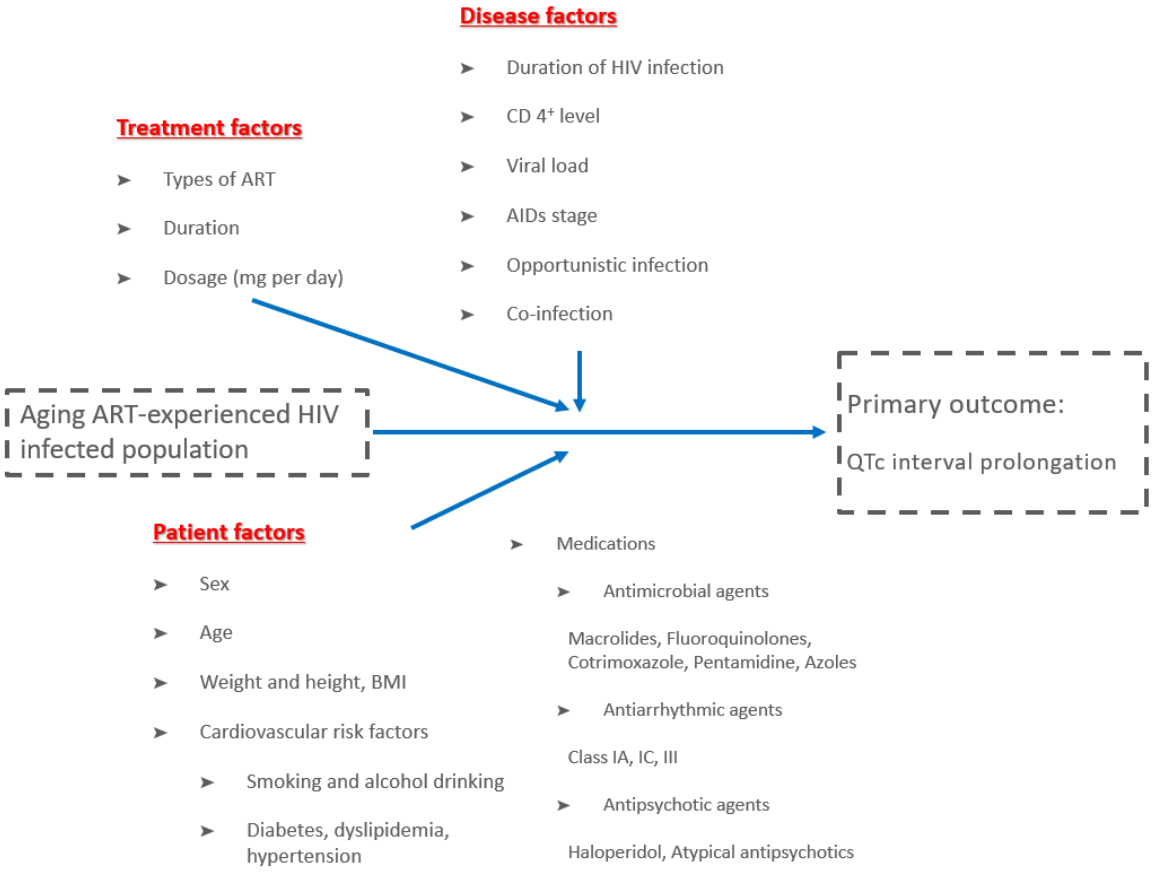


Figure 1. Conceptual framework.

1.4 Expected Benefits and Application

Because of the fact that the current evidences of an association between the potential risk factors in HIV infected patient and the QTc interval prolongation are still controversial; besides, there are few studies related to the aging population and the current HAART regimens. These limited data made many physicians treat and choose ART for aging HIV infected patient difficultly especially when their patients have other risk factors for or previously have the QTc interval prolongation.

This study will provide additional data to answer these debated issues and guide the direction of the future studies.

1.5 Ethical Consideration

1.5.1 Principle of Respect for Autonomy

We use the data from ECG and medical record without disclosing patient identity and the personal data will not show to other persons who is not related to the research; hence, we can keep the patient autonomy.

1.5.2 Principle of Beneficence and Nonmaleficence

The result of this study will provide the information about an association between ART and the QTc interval prolongation which can guide an appropriated management for this group of patients. Besides, this study uses the data from medical record without any procedure, so there is no harm to the patients.

1.5.3 Justice

We include the patients with the same including and excluding criteria.

1.6 Limitation of the Study

- No clinical correlation
- No temporal relationship

CHAPTER II

LITERATURE REVIEW

2.1 General Knowledge

As mentioned in the background, many studies are conducted to find the risk factors of the QTc interval prolongation in HIV infected patients. The study of Chinello et al. (2007) shown the association between patients taking nelfinavir, efavirenz, methadone, cotrimoxazole or an excessive amount of alcohol and an increased risk of the QTc interval prolongation. [1] Sani et al. (2005) was found that the QTc interval was more prolong with a higher HIV stage, and longer duration of infection. [4] Conversely, Shavadia et al. (2012) was found no correlation between HIV infection duration, HIV stage and CD4 count. [2] In 2013, Moreno et al. was found the association of older age, cardiovascular risks (hypertension, dyslipidemia and alcohol), duration of ARTs and the prolongation of QTc interval. [3]

In addition, there are more studies conducted in order to find the association between ARTs and the QTc interval prolongation. These are a review of related literatures categorized by class of ARTs.

2.2 Protease inhibitors

In terms of effect of ART on QTc interval, Protease inhibitors (PIs) are the most available data ART at the present. In 2007, Chinello et al. conducted the nested case-control study in HIV infected patients. They found from the multivariable analysis that Nelfinavir and Efavirenz are the risk factors of QTc prolongation (QTc > 440 ms) especially when use with Zidovudine (the risk was three times higher than use Nelfinavir or Efavirenz alone) while other PIs, Nevirapine and nucleoside reverse transcriptase inhibitors (NRTIs) are not increase risk of QTc prolongation. [1]

Shavadia et al. (2012) found in their case-control study using data from African HIV cohort that ART-experienced arm has significantly more patients with QTc prolongation than ART-naïve arm (16.2% vs 6.9%) and there is no difference in

prevalence of QTc prolongation between patients receiving PI-based regimen and NNRTI-based regimen. However, they did not mention the name of ART use by patient in the study. [2] In the same year, Zhang et al. (2012) published a randomized, double-blind, placebo- and positive-control (Moxifloxacin), 4-way crossover trial of Ritonavir-boosted Saquinavir in therapeutic and supratherapeutic doses in healthy participants found that the QTc interval was significantly increase in both dosage of Saquinavir. [7]

Although many studies support PIs as a risk factor of the QTc prolongation, more studies show the negative results. There are two cross-sectional studies: one is from Charbit et al. (2009) which analyzed data from 956 HIV-infected patients (129 patients with QT prolongation and 38 patients if QTc was corrected) with multivariable linear model and found that PIs (Ritonavir, Lopinavir and Atazanavir), NRTIs (Lamivudine, Tenofovir and Abacavir) and NNRTIs (Efavirenz and Nevirapine) did not significantly association with QTc prolongation. [13] Another is from Moreno et al. (2013) which used multivariate analysis in 194 asymptomatic HIV-infected patients (24 patients with QTc prolongation) and found no association between PIs (Atazanavir and Lopinavir/Ritonavir) and NNRTIs. In their analysis, moreover, shown that Atazanavir was associated was associated with a lower likelihood of having a prolonged QTc (OR 0.11, 95% CI: 0.02–0.5; p = 0.008). [3]

Busti et al. (2006) and Gianotti et al. (2007) conducted a prospective study in HIV-infected patients (21 and 75 patients in each study respectively) who were going to initiate Atazanavir. They found that Atazanavir had no association with QTc prolongation. However, the QRS interval, but not PR interval, increased during treatment with boosted or unboosted atazanavir by a median 5ms (interquartile range 0–9; P<0.0001) in the study of Gianotti et al. (2007). [10, 14] Last but not least important are two randomized-control trials. First, the crossover study of Sarapa et al. (2008) between a single-dose Ritonavir 100 mg, placebo and Moxifloxacin in 65 healthy subjects which found no difference change in QTc duration between Atazanavir and placebo over 12 hours post dose. [20] Second, Damle et al. (2009) conducted a randomized, 4-way crossover, partially-blind study of Nelfinavir in a standard and supratherapeutic dose compared

with placebo and Moxifloxacin which also found no significantly change of QTc interval in 4 days. [21]

Soliman et al. (2011) published a randomized, open-labeled study in 3,719 participants compared an effect of boosted-PI regimens, unboosted-PI regimens and NNRTIs regimens on QTc and PR interval. They found that there was no difference of the QTc interval change in all groups but the PR interval was increase significantly in both PI groups compared to NNRTI group. [11]

Charbit et al. (2011) reported their study of the prevalence and the extent of prolongation of PR and QRS intervals related to antiretroviral therapy. They reported that PIs were the independent predictor of increase in the duration of the PR interval (the adjusted OR of first-degree AV block and complete bundle branch block were 1.62 (95% CI 0.90–2.89; P = 0.10) and 2.71 (95% CI 1.10–7.13; P = 0.03). Moreover, PIs were also the independent predictor of an increase in the duration of the QRS interval, the adjusted QRS-interval duration was 2.6 msec longer (95% CI 1.4–3.9; P = 0.0004). [12]

2.3 Non-Nucleoside Reverse Transcriptase Inhibitors

In addition to three cross-sectional studies (two studies, Chinello et al. and Shavadia et al., with a positive association and one study, Charbit et al., with no association) mentioned in PIs sections, [1, 2, 13] there are others controversial evidences of the effect of NNRTIs on QTc prolongation. In the beginning of NNRTIs era, the first case of QTc prolongation from NNRTIs was reported by Castillo et al. (2002) which happened in HIV-infected African-American woman with normal EKG initiated an ART with Lamivudine, Zidovudine, Abacavir and Efavirenz. Few hours after the first dose, without after dose EKG, she presented with syncope and her EKG shown QTc prolongation (QTc interval = 580 msec) and multiple episodes of Torsade de Point treated with temporary pace maker. Seventy-two hours after discontinuation of all drugs, her QTc interval was become normal and she was restarted an ART with Stavudine, Lamivudine, Nelfinavir and Atovaquone without any recurrence QTC prolongation. [8]

Abdelhady et al. (2016) studied an effect of cytochrome P450 (CYP) enzyme, CYP2B6 (the enzyme that eliminate Efavirenz), which is polymorphically expressed. They found that Efavirenz demonstrated a gene-dose effect for QTc prolongation in healthy volunteers with a CYP2B6*6/*6 (a polymorphism with less clearance of Efavirenz). [9]

There are three randomized, placebo- and active-controlled, crossover studies on others NNRTIs and all of these studies shown no significant association between NNRTIs and QTc prolongation; namely, a study of Etravirine conducted by Peeters et al. (2008), a study of Lersivirine in a supratherapeutic dose conducted by Vouvahis et al. (2013) and a study of single-dose Doravirine conducted by Khalilieh et al. (2017). [22-24]

2.4 Integrase Inhibitors

Integrase inhibitors are relatively new ART. There are only 3 agents commercially using at the present; including, Raltegravir, Elvitegravir and Dolutegravir. Besides, there are other agents that now under developing; for instance, Cabotegravir and Bictegravir. Because of the fact that being newly developed drugs, there are only 3 randomized, placebo- and active-controlled, crossover studies on the supratherapeutic dose Integrase inhibitors. Firstly, the study of Raltegravie conducted by Iwamoto et al. (2008) shown no volunteers in Raltegravir group developed QTc prolongation and changed more than 30 msec. [15] The second study of Chen et al. (2012) on Dolutegravir [16] as well as the third study of Lou et al. (2016) on Cabotegravir also shown no difference change in QTc interval after Integrase inhibitors administration. [17]

2.5 CCR-5 Receptor Inhibitors

To date, there are three CCR-5 inhibitors developed, including Maraviroc which used in clinical practice, Vicriviroc which is in phase III study and Aplaviroc which was discontinued in further development due to its severe liver toxicity. The only two randomized, placebo- and active-controlled, studies were conducted by Davis et al.

(2008) on single-dose Maraviroc and O'Mara et al. (2010) on therapeutic dose Vicriviroc which found no effect of these drugs on QTc interval significantly. [18, 19]

Table 1. Literature review

Authors (published year)	Study Design	Agents	Number (case/control) (expose/nonexp)	Results
Protease inhibitors				
Chinello et al. (2007)	case-control case: control 64: 256	Nelfinavir Atazanavir Lopinavir Other PIs NRTIs	16/10 15/2 38/8 10/3 20/4	OR 6.61 (95% CI = 1.79–24.38; P = 0.005) OR 0.78 (95% CI = 0.12–4.93; P = 0.789) OR 1.78 (95% CI = 0.48–6.58; P = 0.388) OR 3.27 (95% CI = 0.64–16.79; P = 0.157) OR 1.49 (95% CI = 0.36–6.11; P = 0.579)
Shavadia et al. (2012)	case-control	PI-based regimen NNRTI-based regimen	130/130	16.2% vs 6.9% OR 2.5 (95% CI = 1.01–6.67; P = 0.02)
Zhang et al. (2012)	randomized, control, crossover	Saquinavir/r (standard) Saquinavir/r (supratherapeutic)	Enrolled 66 Complete 56	Greatest mean increase = 18.9 ms 12 hr post dose (upper 95% CI = 22) Greatest mean increase = 30.2 ms 20 hr post dose (upper 95% CI = 33.4)
Charbit et al. (2008)	cross-sectional	Ritonavir, Lopinavir and Atazanavir Lamivudine, Tenofovir and Abacavir	440/516 701/220 Total = 956	Diff QT = 0 (95% CI = -2.3–2.2; P = 0.99) Diff QT = 2.8 (95% CI = -0.1–5.7; P = 0.12)
Moreno et al. (2013)	cross-sectional	Atazanavir Lopinavir/r	2/50 1/12 Total = 194	P = 0.02 P = 1
Busti et al. (2006)	prospective	Atazanavir	21	Mean diff QTc 2 hr = 3.19 ms (95% CI = -0.47–6.85; P = 0.084) Mean diff QTc 1 mo = -1.5 ms (95% CI = -5.50–2.46; P = 0.43)
Gianotti et al. (2007)	prospective	Atazanavir	75	QTc interval was not statistically different from baseline.
Sarapa et al. (2008)	randomized, control, crossover	Ritonavir	Enrolled 65 Complete 65	Largest mean QTc increase 0.16 ms (90% CI = -1.38–1.69)
Damle et al. (2009)	randomized, control, crossover	Nelfinavir (standard) Nelfinavir (supratherapeutic)	Enrolled 68 Complete 66	No clinically relevant effect on the QTc interval on day 1 and d4 Mean diff QTc < 5 ms (upper 90% CI < 10 ms)
Soliman et al. (2011)	randomized, open-labeled	Boosted-PIs (Saquinavir, Lopinavir, Atazanavir, etc.) Nonboosted-PIs NNRTIs	236, 548, 188, 184 742 1821	QTc interval in boosted PIs was 1.5 ms lower than the NNRTI group (P = 0.04)

Table 1. Literature review.

Table 1 (continued). Literature review.

Table 1. Literature review				
Authors (published year)	Study Design	Agents	Number (case/control) (expose/nonexp)	Results
Non-Nucleoside Reverse Transcriptase Inhibitors				
Castillo et al. (2002)	case report	Efavirenz		QTc interval = 580 ms Multiple episodes of Torsade de Point
Chinello et al. (2007)	case-control	Efavirenz Nevirapine	56/22 57/8 Case 64 Control 256	OR 4.82 (95% CI = 1.54–15.11; P = 0.007) OR 1.63 (95% CI = 0.47–5.69; P = 0.445)
Shavadia et al. (2012)	case-control	PI-based regimen NNRTI-based regimen	130/130	16.2% vs 6.9% OR 2.5 (95% CI = 1.01–6.67; P = 0.02)
Abdelhady et al. (2016)	experimental	Efavirenz (CYP2B6*6/*6) Efavirenz (CYP2B6*1/*6) Efavirenz (CYP2B6*1/*1) *CYP2B6*6/*6: polymorphism with less EFV clearance	5 15 37	The largest mean time-matched diff QTc in the CYP2B6*6/*6 genotype at 6 hr = 14 ms (95% CI = 1-27) at 12 hr = 18 ms (95% CI = –4-40) at 18 hr = 6 ms (95% CI = –1-14)
Charbit et al. (2008)	cross-sectional	Efavirenz and Nevirapine	289/667 Total = 956	Diff QT = -0.4 (95% CI = -2.9–2.1; P = 0.75)
Peeters et al. (2008)	randomized, control, crossover	Etravirine	Enrolled 41 Complete 37	Upper 90% CI < 10 ms at all time points (mean time-matched)
Vouvahis et al. (2012)	randomized, control, crossover	Lersivirine (supratherapeutic)	Enrolled 48 Complete 48	Upper 90% CI < 10 ms at all time points (mean time-matched)
Khalilieh et al. (2017)	randomized, control, crossover	Doravirine	Enrolled 45 Complete 39	Upper 90% CI < 5.42 ms at all time points

Table 1 (continued). Literature review.

Table 1. Literature review				
Authors (published year)	Study Design	Agents	Number (case/control) (expose/nonexp)	Results
Integrase Inhibitors				
Iwamoto et al. (2008)	randomized, control, crossover	Raltegravir	Enrolled 31 Complete 31	Both Raltegravir and placebo groups no QTcF values >450 ms no change from baseline >30 ms
Chen et al. (2012)	randomized, control, crossover	Dolutegravir	Enrolled 42 Complete 38	The maximum QTc change = 1.99 ms (90% CI = 0.55–4.53)
Lou et al. (2016)	randomized, control, crossover	Cabotegravir	Enrolled 42 Complete 36	Upper 90% CI < 10 ms at all time points (mean time-matched)
CCR-5 Receptor Inhibitors				
Davis et al. (2008)	randomized, control, crossover	Maraviroc	Enrolled 61 Complete 57	Mean diff QTc = 3.6 ms (90% CI = 1.5–5.8)
O'Mara et al. (2010)	randomized, control	Vicriviroc (standard and supratherapeutic)	Enrolled 200 Complete 193	No clinically significant effect on the QT/QTc interval
PR and QRS interval				
Gianotti et al. (2007)	prospective	Atazanavir	75	QRS increase statistically different. 5 ms (IQR = 0–9; P<0.0001) PR interval: not statistically different.
Soliman et al. (2011)	randomized, open-labeled	Boosted-PIs (Saquinavir, Lopinavir, Atazanavir, etc.) Nonboosted-PIs NNRTIs	236, 548, 188, 184 742 1821	PR interval was increased significantly in PI groups compared to NNRTI group Boosted-PIs 5.11 ms (P <0.01) Nonboosted-PIs 3.00 ms (P <0.01)
Charbit et al. (2011)	cross-sectional	PIs NNRTIs NRTIs Untreated	452 228 711 221 Total = 970	PIs were the independent predictor of increase in the PR and QRS interval adjusted OR of 1st degree AV block = 1.62 (95% CI 0.90–2.89; P = 0.10) adjusted OR of complete BBB = 2.71 (95% CI 1.10–7.13; P = 0.03) adjusted QRS-interval increment = 2.6 ms (95% CI 1.4–3.9; P = 0.0004)

CHAPTER III

MATERIALS AND METHODS

3.1 Study Design

The ECG THAI-HAART study was a nested case-control study. To answer the primary research question, the ECG of all included patients will be interpreted to find the prevalence of the QTc interval prolongation. For the secondary research question, the patients with prolonged QTc interval will be classified as 'case' and the patients without prolongation will be classified as 'control'. The age and sex propensity score matched case-control study in 1:2 ratio will be performed to find the associating factors of the QTc interval prolongation. The study was approved by faculty of medicine, Chulalongkorn university institutional review board. This study was not received a grant from any institute.

3.2 Study Population

The ART-experience HIV infected patients with age of 50 or more in the HIV Netherland Australia Thailand research collaboration (HIV-NAT) who have digital ECG recorded from January 2019 to November 2019 were included. Patients who are pacemaker-dependent, have a right or left bundle branch block, established coronary artery disease and usage of the known QTc interval prolonging drugs [Antibiotics (Macrolides, Fluoroquinolones, Cotrimoxazole, Pentamidine and Azoles); antiarrhythmic agents class IA, IC, III; antipsychotic agents] in the period of ECG record were excluded.

3.3 Inclusion and Exclusion Criteria

3.3.1 Inclusion Criteria

- ART-experience HIV infected patient
- Age ≥ 50
- Have a digital ECG record

3.3.2 Exclusion Criteria

- Pacemaker-dependent patient
- Right bundle branch block
- Left bundle branch block
- Established coronary artery disease
- Currently use of established QTc interval prolonging drugs
    - Antimicrobial agents
        - Macrolides
        - Fluoroquinolones
        - Cotrimoxazole
        - Pentamidine
        - Azoles
    - Antiarrhythmic agents class IA, IC, III
    - Antipsychotic agents
        - Haloperidol
        - Atypical antipsychotics

3.4 Research Sequence

1. Performed the literatures review to study the existing and related data
2. Write the research protocol
3. IRB submission to the ethical committee
4. Write the letter to the HIV-NAT for permission to collecting patient data.
5. Collecting data and interpreting ECG after the ethical committee permission
6. Analyzing the data
7. Reporting and publishing the research results

3.5 Data collection

All the following data and ECG record will be collected.

3.5.1 Patient Factors

- Sex
- Age
- Weight and height, BMI
- Cardiovascular risk factors
    - Smoking and alcohol drinking
    - Diabetes, dyslipidemia, hypertension
- Medication [Duration (month), dosage (mg per day)]
    - Antimicrobial agents
        - Macrolides, Fluoroquinolones,
        - Cotrimoxazole, Pentamidine, Azoles
    - Antiarrhythmic agents
        - Class IA, IC, III
    - Antipsychotic agents
    - Haloperidol, Atypical antipsychotics

3.5.2 Disease Factors

- Duration of HIV infection
- CD 4+ level
- Viral load
- HIV stage (CDC)
- Opportunistic infection
- Co-infection

3.5.3 Treatment Factors

- Types of ART
- Duration (month)
- Dosage (mg per day)

3.5.4 ECG Records and Measurements

- QTc interval (ms)
- PR interval (ms)
- QRS duration (ms)
- AV block
- Heart rate (bpm)
- Rhythm

3.6 Data Analysis

3.6.1 ECG Analysis

The standard surface 12-lead ECGs record with the Philips PageWriter Trim II ECG Machine and display on a digital screen which can be zoom in and zoom out for an accurately measure. The ECGs trace at rate 25 mm/s paper speed and at 10 mm/mV amplitude. [25] After recorded, the ECG data will be transferred to analyzed at the data center of the King Chulalongkorn memorial hospital cardiology unit by cardiologist (Figure 2). The ECG re-analyzed will be done at 1 month after the first analysis for intra-observer testing. All intervals will measure in limb lead II. Precordial lead V3 will be used, if limb lead II is uninterpretable. If precordial V3 is still uninterpretable, precordial lead V5 and then V6 will be used. The QTc interval, PR interval and QRS complex duration are measured with an automatic ECG analysis software with manual correction. The QT interval measures from the start of the QRS complex to the end of the T wave which will be indicated with the tangent method (Figure 3). [26] The PR interval measures from the start of the P wave to the start of the QRS complex. Last, the QRS complex duration measures from the start of the QRS complex to the J point. In ECG with an irregular rate, the longest and shortest QT interval will be measured and calculated for the mean QT interval.

The QT interval will be corrected with heart rate by the most three accurate and popular formulas namely Bazett's formula (QTc = QT/RR1/2), Fridericia's formula (QTc = QT/RR1/3) and Framingham's formula (QTc = QT +

0.154(1-RR)). The QTc interval prolongation define as QTc interval > 450 millisecond (ms) in men and > 460 ms in women. [25, 27] For the final analysis, QTc interval from the Bazett's formula will be used if the HR was 90 bpm or less and the Fridericia's formula will be used if HR was more than 90 bpm for prevent QT interval overcorrection. The PR interval prolongation defines as PR interval > 200 ms, and the QRS duration defines as QRS duration > 120 ms.

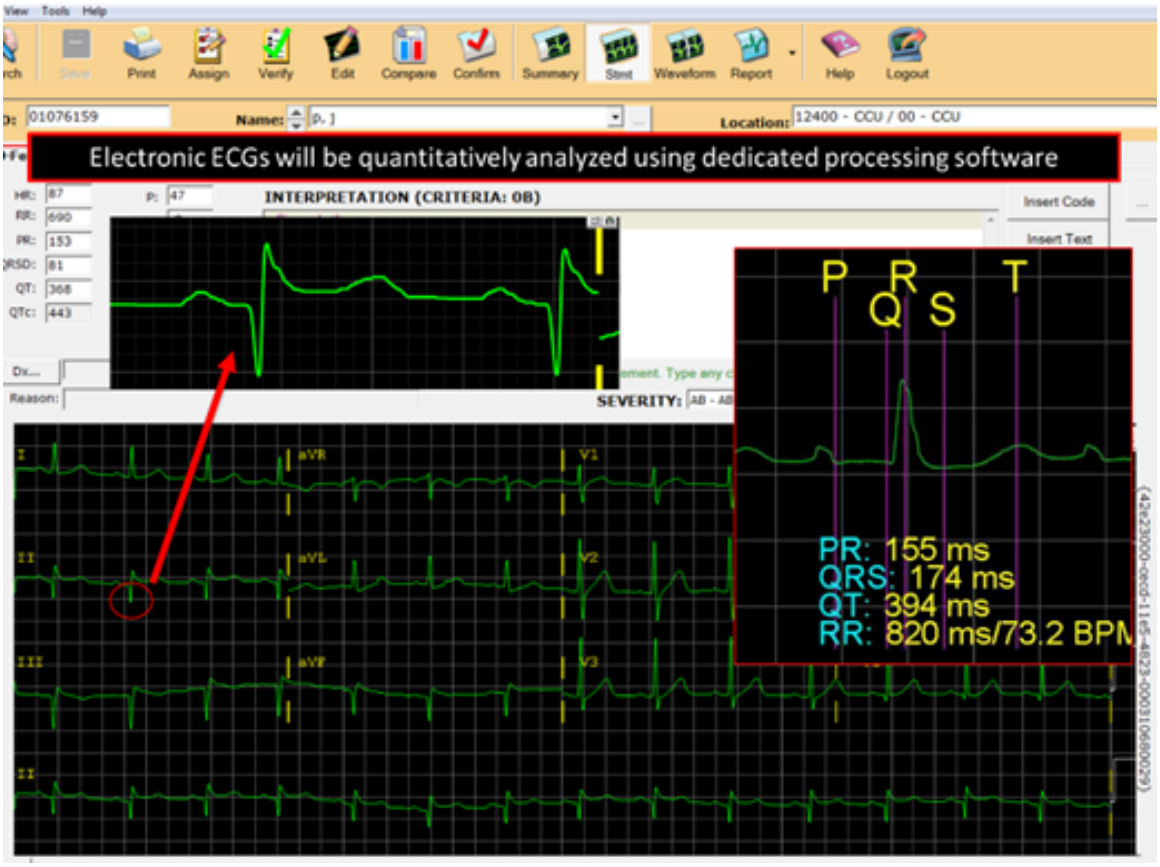


Figure 2. Example of ECG analysis program.

\

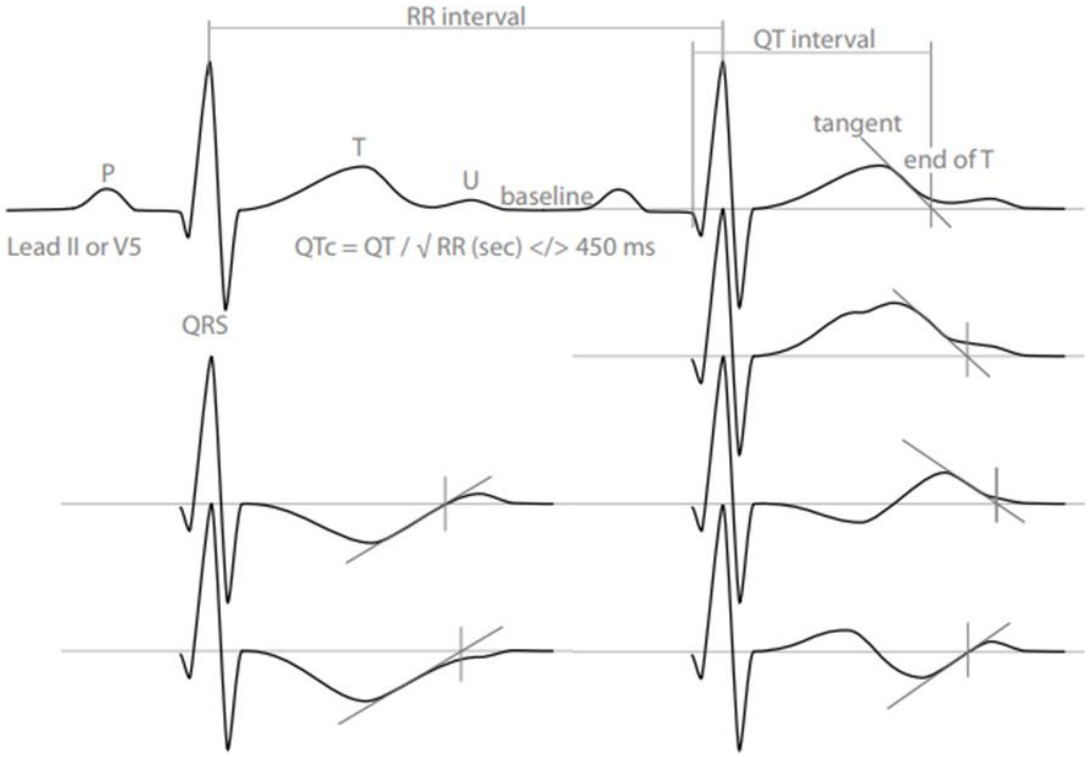


Figure 3. End of T wave indicated with Tangent method.

3.6.2 Statistical Analysis

The sample size was calculated with an expected exposure rate 0.89 in cases and 0.82 in controls. [1] The ratio of control to case was 2 to 1. The sample size of 297 required to find the association of exposures between case and control with a level of statistical significance of 0.05 and 80% power.

The continuous variables were demonstrated as a mean and SD or medians and range. The categorical variables were demonstrated as a frequency and percentage. The possible associating factors of QTc interval prolongation were analyzed by univariable and then multivariable analysis adjusted with the known and potential confounding factors using binary logistic regression model. The outcomes were reported as an adjusted odds ratio (OR)

and 95% CI. The intra-observer and inter-observer variability were analyzed by two-way random effects model, intraclass correlation coefficient (ICC) more than 0.90. All statistics were performed with SPSS Statistics version 22.0 and STATA/SE version 14.1.

3.7 Sample Size Calculation

[28]

$$\text{Sample size (n)} = \frac{r+1}{r}\frac{(p^*)(1-p^*)(Z_\beta + Z_{\alpha/2})^2}{(p_1 - p_2)^2}$$

where

n = {[(4 + 1)/4] x 0.855 x (1 - 0.855) x (0.84 + 1.96)2} / 0.072 = 248

r (ratio of control to cases) = 4

$Z\alpha/2$ (standard normal variate at 5% type I error, P<0.05) = 1.96

$Z\beta$ (standard normal variate at 20% type II error, power 80%) = 0.84

p* (average proportion exposed) = (0.89 + 0.82)/2 = 0.855 [1]

[proportion of exposed cases + proportion of control exposed/2]

p1 – p2 (different in proportion expected) = 0.89 – 0.82 = 0.07

3.8 Administration and time schedule

Activity	Duration
1. Plan the study including IRB	March 2019 - December 2019
2. Data collection	January 2020
3. Data analysis	January 2020
4. Report study	February 2020

3.9 Keywords

- HIV infection
- AIDs
- HAART
- Antiretroviral agent
- Aging
- Torsades de Point
- QT interval
- QTc interval prolongation
- PR interval
- QRS duration
- Electrocardiogram

CHAPTER IV

STUDY RESULTS

4.1 Baseline Characteristics

From January 2019 to November 2019, 460 patients were enrolled and 47 patients were excluded due to established coronary artery disease 15 cases, had left or right bundle branch block 17 cases and used known QT interval prolonging drugs 15 cases. (Figure 4) 413 patients with the mean age of 56.0 +/- 5.5 (range 50.0-76.0) years old were included. There were 249 (60.3%) male patients. 272 (65.9%), 107 (25.9%) and 34 (8.2%) patients were normal BMI, overweight and underweight, respectively. There were 164 (39.7%) patients with hypertension, 56 (13.6%) patients with diabetes mellitus, 290 (70.2%) patients with dyslipidemia and 7 (1.7%) patients with history of stroke. The patients currently drinking alcohol and smoking were 71 (17.2%) and 59 (14.3%) patients, respectively. The mean duration of infection was 234.6 +/- 68.3 (3.0-386.0) months. There was no patient with AIDS and most of the patients were well disease control with the mean CD4 level was 640.46 +/- 242.98 cells/mcl and 401 (97.1%) patients were undetectable viral load. 154 (37.3%) and 191 (46.2%) patients were in the CDC stage A and B. Most of the patients, 405 (98.1%), were on 3-drug regimens; 338 (93.9%) patients were on 2 NRTIs plus one of the following: NNRTI, boosted PI, integrase inhibitor (II) or CCR-5 co-receptor inhibitor regimen and 17 (4.2%) patients were on 1 NRTI, 1 NNRTI and 1 boosted PI regimen. Eight (1.9%) patients were on 2-drug regimen: 1 NNRTI plus 1 boosted PI. (Table 2)

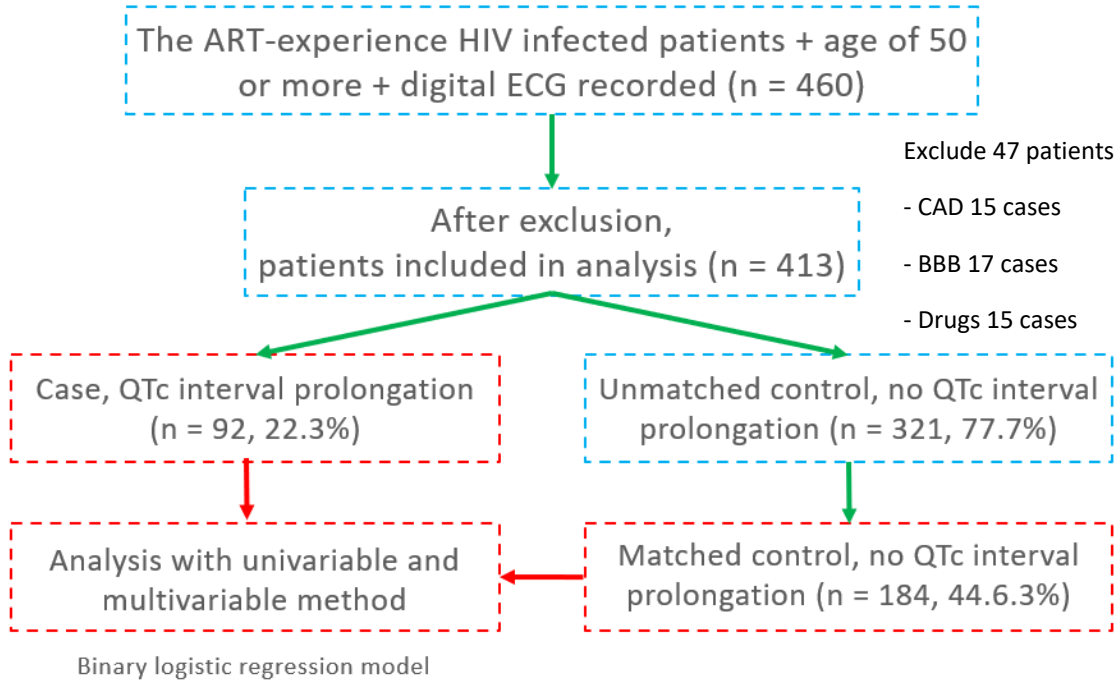


Figure 4. Enrollment flow diagram.

Table 2. Baseline characteristics of all patients, cases and controls.

Table 2. Baseline characteristics of all patients, cases and controls						
Variables	All case (n=413)	QTc Case (n=92)	Unmatched case (n=321)	Matched case (n=184)	p-value	
					Unmatched	Matched
Age	56.06 ± 5.49	57.62 ± 6.13	55.62 ± 5.21	57.36 ± 5.8	0.002*	0.73
Gender						
Male	249 (60.3%)	48 (52.2%)	201 (62.6%)	97 (52.7%)	0.071	0.932
Female	164 (39.7%)	44 (47.8%)	120 (37.4%)	87 (47.3%)		
BMI						
18.5-24.99	272 (65.9%)	57 (62%)	215 (67%)	122 (66.3%)	0.344	0.394
<18.5	34 (8.2%)	6 (6.5%)	28 (8.7%)	17 (9.2%)		
>=25	107 (25.9%)	29 (31.5%)	78 (24.3%)	45 (24.5%)		
Hypertension	164 (39.7%)	47 (51.1%)	117 (36.4%)	73 (39.7%)	0.011*	0.071
Diabetes	56 (13.6%)	16 (17.4%)	40 (12.5%)	25 (13.6%)	0.223	0.402
Dyslipidemia	290 (70.2%)	62 (67.4%)	228 (71%)	137 (74.5%)	0.501	0.217
Stroke	7 (1.7%)	2 (2.2%)	5 (1.6%)	2 (1.1%)	0.686	0.476
Alcohol	71 (17.2%)	12 (13%)	59 (18.4%)	31 (16.8%)	0.232	0.411
Smoking Currently	59 (14.3%)	15 (16.3%)	44 (13.7%)	28 (15.2%)	0.754	0.814
Duration of Infection (Month)	234.57 ± 68.34	245 (189, 273)	245 (200, 281)	244.5 (199, 280)	0.546	0.694
CD4 Level	640.46 ± 242.98	630.5 (505, 750)	601 (479, 770)	590.5 (481, 754)	0.307	0.282
Viral Load						
<40	401 (97.1%)	87 (94.6%)	314 (97.8%)	179 (97.3%)	0.101	0.255
>=40	12 (2.9%)	5 (5.4%)	7 (2.2%)	5 (2.7%)		
CDC Stage						
A	154 (37.3%)	33 (35.9%)	121 (37.7%)	70 (38%)	0.665	0.877
B	191 (46.2%)	46 (50%)	145 (45.2%)	86 (46.7%)		
C	68 (16.5%)	13 (14.1%)	55 (17.1%)	28 (15.2%)		
NRTI						
TDF	284 (68.8%)	63 (68.5%)	221 (68.8%)	121 (65.8%)	0.946	0.652

Table 2. Baseline characteristics of all patients, cases and controls						
Variables	All case (n=413)	QTc Case (n=92)	Unmatched case (n=321)	Matched case (n=184)	p-value	
					Unmatched	Matched
3TC	225 (54.5%)	58 (63%)	167 (52%)	113 (61.4%)	0.061	0.793
FTC	179 (43.3%)	34 (37%)	145 (45.2%)	63 (34.2%)	0.161	0.656
ABC	70 (16.9%)	16 (17.4%)	54 (16.8%)	35 (19%)	0.898	0.742
ZDV	17 (4.1%)	5 (5.4%)	12 (3.7%)	10 (5.4%)	0.470	1
TAF	16 (3.9%)	5 (5.4%)	11 (3.4%)	1 (0.5%)	0.379	0.009*
NNRTI						
None	142 (34.4%)	28 (30.4%)	114 (35.5%)	65 (35.3%)	0.096	0.433
RPV	152 (36.8%)	29 (31.5%)	123 (38.3%)	67 (36.4%)		
EFV	80 (19.4%)	21 (22.8%)	59 (18.4%)	32 (17.4%)		
NVP	39 (9.4%)	14 (15.2%)	25 (7.8%)	20 (10.9%)		
PI						
None	279 (67.6%)	69 (75%)	210 (65.4%)	113 (61.4%)	0.212	0.125
ATV	72 (17.4%)	11 (12%)	61 (19%)	38 (20.7%)		
LPV	53 (12.8%)	9 (9.8%)	44 (13.7%)	28 (15.2%)		
DRV	9 (2.2%)	3 (3.3%)	6 (1.9%)	5 (2.7%)		
II						
None	390 (94.4%)	84 (91.3%)	306 (95.3%)	180 (97.8%)	0.056	0.058
RAL	1 (0.2%)	1 (1.1%)	0 (0%)	0 (0%)		
DTG	21 (5.1%)	6 (6.5%)	15 (4.7%)	4 (2.2%)		
EVG	1 (0.2%)	1 (1.1%)	0 (0%)	0 (0%)		
CCR5 inh.						
None	412 (99.8%)	91 (98.9%)	321 (100%)	184 (100%)	0.061	0.157
MVC	1 (0.2%)	1 (1.1%)	0 (0%)	0 (0%)		

Value presented as mean ± SD. or median (IQR) and n (%).

P-value corresponds to Independent t test or Mann-Whitney test and Chi-square test.

BMI = body mass index; CDC = Centers for Disease Control; NRTI = nucleoside reverse transcriptase inhibitor; TDF = Tenofovir Disoproxil Fumarate; 3TC = Lamivudine; FTC = Emtricitabine; ABC = Abacavir; ZDV = Zidovudine; TAF = Tenofovir Alafenamide; NNRTI = non-nucleoside reverse transcriptase inhibitor; RPV = Rilpiverine; EFV = Efavirenz; NTV = Nevirapine; PI = Protease inhibitor; ATV = Atazanavir; LPV = Lopinavir; DRV = Darunavir; II = Integrase inhibitor; RAL = Raltegravir; DTG = Dolutegravir; EVG = Elvitegravir; CCR5 = CCR5 co-receptor antagonist; MVC = Maraviroc

4.2 ECG Data

The QTc interval prolongation was found in 92 (22.3%) patients (Figure 5). The mean QTc interval by Bazett's formula was 434.4 +/- 27.5 (range 352 to 532) ms. The severe QTc interval prolongation (> 500 ms) was found in 2 patients. Every patient was sinus rhythm except one was atrial flutter. The mean heart rate was 67.2 +/- 10.9 bpm. There was 41 (9.9%) patients with first degree AV block and none with second or higher graded AV block. The QRS duration > 120 ms was found in 15 (3.6%) of patients. (Table 3) The intra-observer and inter-observer variability ICC were 0.92 (95% CI 0.90 to 0.93) and 0.90 (95% CI 0.88 to 0.92), respectively.

Table 3. ECG data of all patients, cases and controls.

Table 3. ECG data of all patients, cases and controls						
Variables	All case (n=413)	QTc Case (n=92)	Unmatched case (n=321)	Matched case (n=184)	p-value	
					Unmatched	Matched
Rhythm						
SR	412 (99.8%)	92 (100%)	320 (99.7%)	183 (99.5%)	0.592	0.479
AFL	1 (0.2%)	0 (0%)	1 (0.3%)	1 (0.5%)	0.592	0.479
Rate	67.24 ± 10.95	71.74 ± 10.88	65.95 ± 10.64	66.24 ± 10.36	<0.001*	<0.001*
PR Interval	169.56 ± 23.25	169.64 ± 21.32	169.53 ± 23.8	168.98 ± 25.14	0.969	0.830
First degree AV block	41 (9.9%)	7 (7.6%)	34 (10.6%)	20 (10.9%)	0.399	0.390
QRS Duration	93.31 ± 13.45	93.52 ± 13.1	93.25 ± 13.57	93.48 ± 14.05	0.866	0.983
QRS prolong (yes)	15 (3.6%)	5 (5.4%)	10 (3.1%)	5 (2.7%)	0.294	0.255
QT Interval	413.44 ± 32.19	433.8 ± 34.37	407.6 ± 29.07	409.64 ± 29.15	<0.001*	<0.001*
Bazett's Formula	434.4 ± 27.52	470.38 ± 14.22	424.08 ± 20.94	427.18 ± 19.5	<0.001*	<0.001*
Fridericia's Formula	426.98 ± 24.21	457.56 ± 16.67	418.22 ± 18.16	420.96 ± 17.3	<0.001*	<0.001*
Framingham's Formula	413.45 ± 32.18	433.83 ± 34.35	407.61 ± 29.05	409.65 ± 29.13	<0.001*	<0.001*
QTc for analysis	433 ± 27	469.58 ± 12.94	423.16 ± 20.67	426.43 ± 19.18	<0.001*	<0.001*
QTc beyond normal	14.73 ± 12.83	14.73 ± 12.83	-	-	N/A	N/A
QTc for analysis (male)	427.89 ± 27.39	467.27 ± 13.99	418.49 ± 20.58	422.44 ± 19.55	<0.001*	<0.001*
QTc for analysis (female)	442.01 ± 24.13	472.09 ± 11.30	430.98 ± 17.15	430.86 ± 17.84	<0.001*	<0.001*

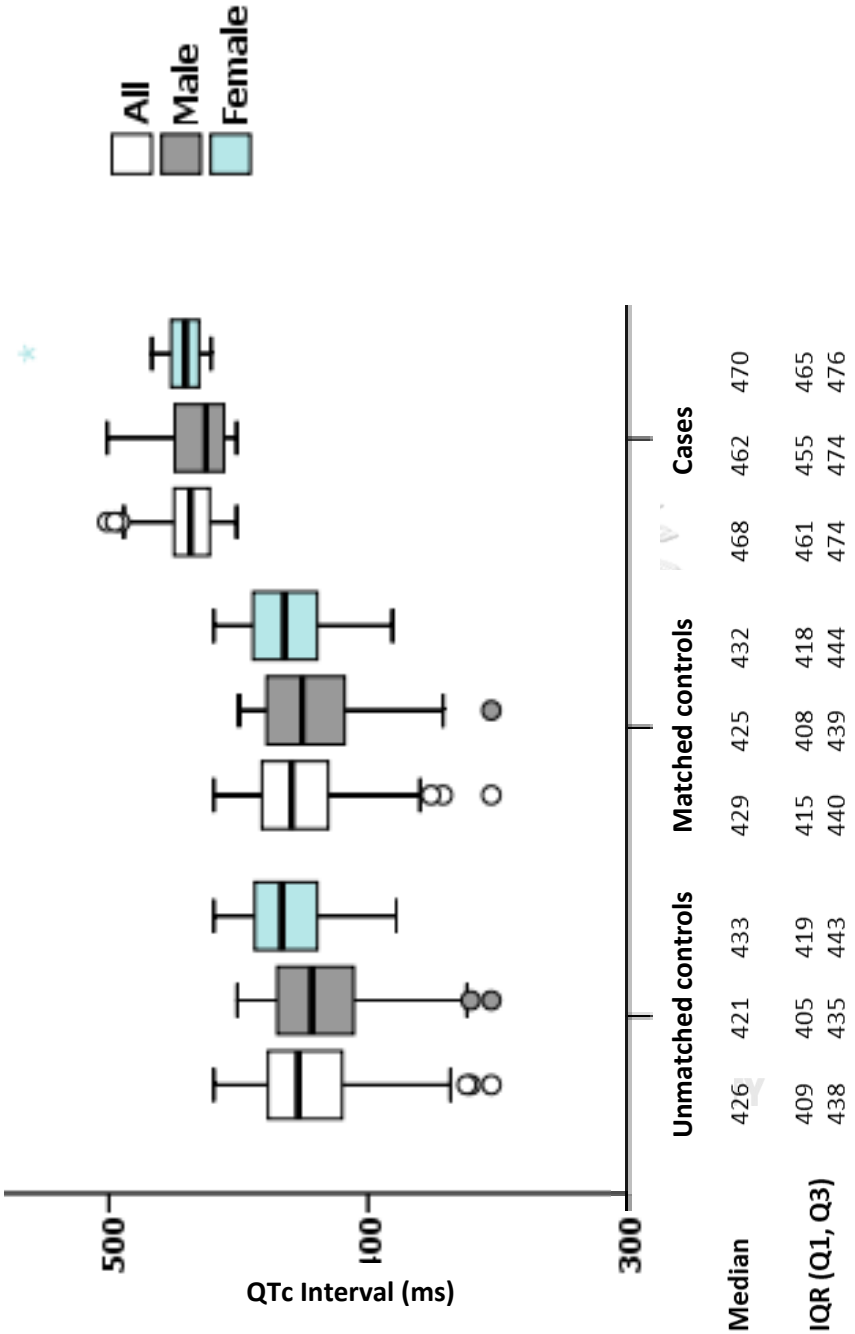


Figure 5. Box and whisker plot of the QTc interval of unmatched controls, matched controls and cases.

4.3 Analytic Results

The baseline characteristics of case and control were demonstrated in table 2. The older age (OR 1.06, 95% CI 1.02-1.11, p = 0.002), hypertension (OR 1.82, 95% CI 1.14-2.91, p = 0.012) and Nevirapine use (OR 2.28, 95% CI 1.05-4.94, p = 0.037) were found to associated with QTc interval prolongation in unmatched analysis but found no association after matching.

The univariable analysis was reported in table 4. The matched case-control found the association of Tenofovir alafenamide and Atazanavir use with the QTc interval prolongation. After adjusted known and possible confounding factors in multivariable analysis, however, there was no factor found to be associated. (Table 5)

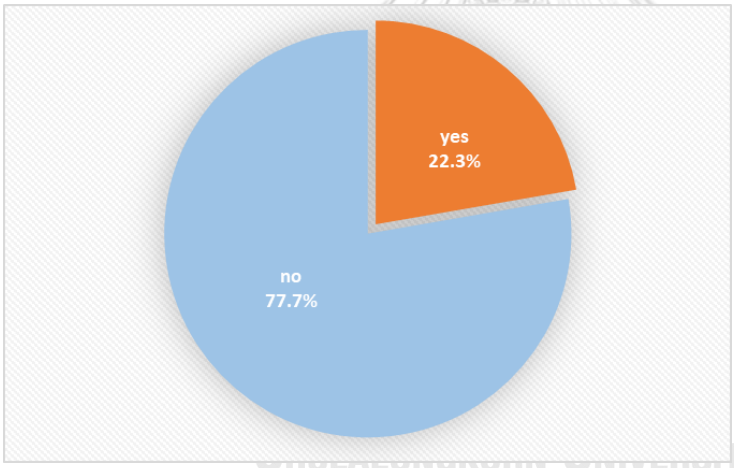


Figure 6. The prevalence of the QTc interval prolongation.

Table 4. Univariable analysis of risk factors for the QTc interval prolongation.

Table 4. Univariable analysis of risk factors for the QTc interval prolongation				
Variables	Unmatched case		Matched case	
	OR (95% CI.)	p-value	OR (95% CI.)	p-value
Age	1.06 (1.02, 1.11)	0.002*	1.01 (0.97, 1.05)	0.729
Gender				
Male	Reference	1	Reference	1
Female	1.54 (0.96, 2.45)	0.072	1.02 (0.62, 1.69)	0.932
BMI				
18.5-24.99	Reference	1	Reference	1
<18.5	0.81 (0.32, 2.05)	0.653	0.76 (0.28, 2.02)	0.576
>=25	1.4 (0.84, 2.35)	0.2	1.38 (0.79, 2.42)	0.263
Hypertension	1.82 (1.14, 2.91)	0.012*	1.59 (0.96, 2.63)	0.072
Diabetes	1.48 (0.79, 2.78)	0.225	1.34 (0.68, 2.65)	0.403
Dyslipidemia	0.84 (0.51, 1.39)	0.502	0.71 (0.41, 1.23)	0.218
Stroke	1.4 (0.27, 7.36)	0.688	2.02 (0.28, 14.59)	0.485
Alcohol	0.67 (0.34, 1.3)	0.234	0.74 (0.36, 1.52)	0.413
Smoking Currently	1.2 (0.63, 2.29)	0.583	1.12 (0.56, 2.24)	0.748
Duration of Infection (Month)	1 (1, 1)	0.804	1 (1, 1)	0.862
CD4 Level	1 (1, 1)	0.341	1 (1, 1)	0.256
Viral Load				
<40	Reference	1	Reference	1
>=40	2.58 (0.8, 8.32)	0.113	2.06 (0.58, 7.3)	0.264
CDC Stage				
A	Reference	1	Reference	1
B	1.16 (0.7, 1.93)	0.56	1.13 (0.66, 1.96)	0.651
C	0.87 (0.42, 1.77)	0.696	0.98 (0.45, 2.14)	0.969
NRTI				
TDF	0.98 (0.6, 1.62)	0.946	1.13 (0.66, 1.93)	0.652
3TC	1.57 (0.98, 2.53)	0.062	1.07 (0.64, 1.8)	0.793
FTC	0.71 (0.44, 1.15)	0.162	1.13 (0.67, 1.9)	0.656
ABC	1.04 (0.56, 1.92)	0.898	0.9 (0.47, 1.72)	0.742
ZDV	1.48 (0.51, 4.31)	0.473	1 (0.33, 3.02)	1

Table 4. Univariable analysis of risk factors for the QTc interval prolongation				
Variables	Unmatched case		Matched case	
	OR (95% CI.)	p-value	OR (95% CI.)	p-value
TAF	1.62 (0.55, 4.79)	0.383	10.52 (1.21, 91.39)	0.033*
NNRTI				
None	Reference	1	Reference	1
RPV	0.96 (0.54, 1.71)	0.89	1 (0.54, 1.87)	0.988
EFV	1.45 (0.76, 2.77)	0.261	1.52 (0.75, 3.09)	0.243
NVP	2.28 (1.05, 4.94)	0.037*	1.62 (0.72, 3.67)	0.242
PI				
None	Reference	1	Reference	1
ATV	0.55 (0.27, 1.1)	0.092	0.47 (0.23, 0.99)	0.046*
LPV	0.62 (0.29, 1.34)	0.226	0.53 (0.23, 1.18)	0.12
DRV	1.52 (0.37, 6.25)	0.56	0.98 (0.23, 4.24)	0.981
II				
None	Reference	1	Reference	1
RAL	1 (0, 1)	1	1 (0, 1)	1
DTG	1.46 (0.55, 3.87)	0.45	3.21 (0.88, 11.69)	0.076
EVG	1 (0, 1)	1	1 (0, 1)	1
CCR5 inhibitor				
None	Reference	1	Reference	1
MVC	1 (0, 1)	1	1 (0, 1)	1

Value presented as Odds ratio (95%CI). P-value corresponds to Logistic regression analysis.

BMI = body mass index; CDC = Centers for Disease Control; NRTI = nucleoside reverse transcriptase inhibitor; TDF = Tenofovir Disoproxil Fumarate; 3TC = Lamivudine; FTC = Emtricitabine; ABC = Abacavir; ZDV = Zidovudine; TAF = Tenofovir Alafenamide; NNRTI = non-nucleoside reverse transcriptase inhibitor; RPV = Rilpiverine; EFV = Efavirenz; NTV = Nevirapine; PI = Protease inhibitor; ATV = Atazanavir; LPV = Lopinavir; DRV = Darunavir; II = Integrase inhibitor; RAL = Raltegravir; DTG = Dolutegravir; EVG = Elvitegravir; CCR5 = CCR5 co-receptor antagonist; MVC = Maraviroc

Table 5. Multivariable analysis of risk factors for QTc interval prolongation.

Table 5. Multivariable analysis of risk factors for QTc interval prolongation				
	Unmatched case		Matched case	
Variables	Adjusted OR (95% CI.)	p-value	Adjusted OR (95% CI.)	p-value
Age	1.06 (1.01, 1.11)	0.021*	-	-
Hypertension	1.71 (1.03, 2.85)	0.039*	1.68 (0.97, 2.92)	0.062
NRTI				
TDF	6.3 (1.06, 37.4)	0.043	4.18 (0.76, 22.95)	0.099
3TC	1 (0, 1)	0.999	1 (0, 1)	0.999
FTC	1 (0, 1)	0.999	1 (0, 1)	0.999
ABC	3.92 (0.61, 25.12)	0.15	3.19 (0.53, 19.24)	0.206
ZDV	3.04 (0.45, 20.57)	0.255	1.82 (0.29, 11.63)	0.525
TAF	1 (0, 1)	0.999	1 (0, 1)	0.999
NNRTI				
None	Reference	1	Reference	1
RPV	1.62 (0.11, 24.57)	0.729	0.99 (0.07, 14.77)	0.994
EFV	2.67 (0.18, 39.23)	0.473	1.86 (0.13, 26.68)	0.646
NPV	3.43 (0.21, 57.5)	0.391	2.04 (0.12, 33.33)	0.618
PI				
None	Reference	1	Reference	1
ATV	1 (0.07, 15.24)	1	0.67 (0.05, 9.87)	0.768
LPV	1.37 (0.08, 22.53)	0.824	0.9 (0.06, 14.66)	0.943
DRV	3.91 (0.19, 79.12)	0.374	1.93 (0.09, 40.16)	0.671
II				
None	Reference	1	Reference	1
DTG	0 (0, 1)	0.999	0 (0, 1)	0.999

Value presented as Odds ratio (95%CI). P-value corresponds to Logistic regression analysis.

NRTI = nucleoside reverse transcriptase inhibitor; TDF = Tenofovir Disoproxil Fumarate; 3TC = Lamivudine; FTC = Emtricitabine; ABC = Abacavir; ZDV = Zidovudine; TAF = Tenofovir Alafenamide; NNRTI = non-nucleoside reverse transcriptase inhibitor; RPV = Rilpiverine; EFV = Efavirenz; NTV = Nevirapine; PI = Protease inhibitor; ATV = Atazanavir; LPV = Lopinavir; DRV = Darunavir; II = Integrase inhibitor; DTG = Dolutegravir

CHAPTER V

Discussion and Conclusion

5.1 Discussion

Compared to the previous reports, our study shows a higher prevalence 22.3% vs 10% to 16%. It seems age is the most possible explanation because the mean age in our study is 56 years old which is 10 to 14 years older. [1-3] The trend that the prevalence increasing with age was showed in Chinello et al. study that reported 9.8% prevalence with the mean age of 42 years old compared to 12.4% prevalence with the mean age of 46 years old in Moreno et al. study. In addition, our unmatched analysis shows that older age is the risk factor of the QTc interval prolongation (OR 1.06, 95% CI 1.02-1.11, p = 0.002). Hypertension is related to the increasing age but no true association with the QTc interval because the association disappeared after matched cases and controls with age and sex.

Previously, many controversial evidences showed the association between the QTc interval prolongation and many factors in HIV infected patients including cardiovascular risks (hypertension, dyslipidemia, alcohol and smoking), duration of HIV infection and the usage of ART particularly PIs and NNRTIs. [1, 2, 7-9] This study, however, found no association from these factors. To our knowledge, there are several known factors that causing the QTc interval prolongation and many of these factors are likely to coincided with HIV infection. While the previous studies may be confounded with these factors, our study was excluded these known factors namely pacing ECG, left and right bundle branch block, patients with established coronary artery disease and the most importantly QTc interval prolonging drugs to eliminating as much as possible confounding factors.

As the evidences from phase 2, phase 3 trials, and meta-analysis; Dolutegravir, a relatively new integrase inhibitor, showed no association with the QTc interval prolongation and no report of adverse cardiovascular event. [20, 27-30] Our study

supports the safety of this drug which is not boosted integrase inhibitor, though only a small case numbers (21/413, 5.1%) used.

There are many strong points of this study. The most important part is that we excluded almost all the known confounding factors, so our results represent a true effect of these possible factors on the QTc interval. Because of the fact that the ECGs in this study were interpreted by the reliable software and confirmed by two cardiologists on computer display. The accuracy of the measurements is trustworthy as showed in the intra-observer ICC = 0.92 (95% CI 0.90 to 0.93) and inter-observer variability ICC = 0.90 (95% CI 0.88 to 0.92). In term of the QTc interval prolongation diagnosis, two of the most acceptable and accurate heart rate correction formulas were use appropriately to reduce overdiagnosis. Last but not least important, our study is the first study focused in the aging HIV infected patients that trend to be more common in the population.

5.2 Limitations

Our study has some limitations. First, despite overall patients' number of the study is sufficient, the number of patients using some drugs is small. This may have an effect on the result accuracy of these drugs. Secondly, a number of patients received the reduced dose regimen to make the dose appropriated for the Asian ethnicity. Thirdly, almost all patients are well disease control, the outcome of the study may not be able to generalized to the whole HIV infected population especially who has AIDs, CD4+ level < 200 or taking medications for treating and preventing opportunistic infections. Lastly, the data was reviewed retrospectively. This may lead to the selection and recall bias and it is also impossible to find the temporal relationship between the exposures and the QTc interval.

5.3 Conclusion

The prevalence of the QTc interval prolongation was higher in aging ART-experience HIV infected patient. Except the older age, there was no other factor including ART use found to associated with the QTc interval prolongation.

REFERENCES

1. Chinello, P.L., F.P.; Angeletti, C., et al., *Role of antiretroviral treatment in prolonging QTc interval in HIV-positive patients.* J Infect, 2007. **54**: p. 597-602.
2. Shavadia, J.S., R.; Yonga, G., et al., *The Influence of Antiretroviral Therapy on the QTc Interval in an African Cohort.* Clin Infect Dis, 2012: p. 448-9.
3. Moreno, T.P.r., I.; Isasti, G., et al., *Prevalence and Factors Associated with a Prolonged QTc Interval in a Cohort of Asymptomatic HIV-Infected Patients.* AIDS Res Hum Retroviruses, 2013. **29**: p. 1995-8.
4. Sani, M.U.O., B.N., *QTc interval prolongation in patients with HIV and AIDS.* J Natl Med Assoc, 2005. **97**: p. 1657-61.
5. Kocheril, A.G.B., S.A.J.; Batsford, W.P., et al., *Long QTc and torsades de pointes in human immunodeficiency virus disease.* PACE, 1997. **20**: p. 2810-6.
6. Nordin, C.K., A.; Beca, S., et al., *Importance of hepatitis C coinfection in the development of QT prolongation in HIV-infected patients.* J Electrocardiol, 2006. **39**: p. 199-205.
7. Zhang, X.J., P.; Cristea, L., et al., *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**: p. 520-9.
8. Castillo, R.P., R.P.; El-Sherif, N., et al., *Efavirenz-Associated QT Prolongation and Torsade de Pointes Arrhythmia.* Ann Pharmacother, 2002. **36**: p. 1006-8.
9. Abdelhady, A.M.S., T.; Thong, N., et al. . 2016; 27: 1206–13, *Efavirenz inhibits the human ether-a-go-go related current (hERG) and induces QT interval prolongation in CYP2B6*6*6 allele carriers.* J Cardiovasc Electrophysiol, 2016. **27**: p. 1206-13.
10. Sebastiano, G.M., M.; Flavia, B., et al., *Prevalence and predictors of long corrected QT interval in HIV-positive patients: a multicenter study.* J Cardiovasc Med, 2017. **18**: p. 539-44.

11. Gianottia, N.G., M.; Galli, L., et al., *Electrocardiographic changes in HIV-infected, drug-experienced patients being treated with atazanavir.* AIDS Res Hum Retroviruses, 2007. **21**: p. 1648-51.

12. Soliman, E.Z.L., J.D.; Roediger, M.P., et al. 2011; 25: 367–77, *Boosted protease inhibitors and the electrocardiographic measures of QT and PR durations.* AIDS, 2011. **25**: p. 367-77.

13. Charbit, B.G., E.; Voiriot, P., et al., *Effects of HIV Protease Inhibitors on Cardiac Conduction Velocity in Unselected HIV-Infected Patients.* Clin Pharmacol Ther, 2011. **90**: p. 442-8.

14. Charbit, B.R., A.; Bollens, D., et al., *Relationship between HIV protease inhibitors and QTc interval duration in HIV-infected patients: a cross-sectional study.* Br J Cli Pharmacol, 2009. **67**: p. 76-82.

15. Busti, A.J.T., J.P.; Peeters, M.J., 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**: p. 317-22.

16. Wu, K.C.Z., L.; Haberlen, S.A., et al., *Predictors of electrocardiographic QT interval prolongation in men with HIV.* Heart, 2019. **105**: p. 559-65.

17. Olarinde, O.Y., O.; Michael, O., *QTc interval prolongation in HIV-negative versus HIV-positive subjects with or without antiretroviral drugs.* Ann Afr Med, 2015. **14**: p. 169-76.

18. Myerson, M.E., K.L.; Eduard, P., et al., *Prolonged QTc in HIV-infected patients: a need for routine ECG screening.* J Int Assoc Provid AIDs Care, 2019. **18**: p. 1-8.

19. Iwamoto, M.K., J.T.; Mistry, G.C., et al., *Raltegravir thorough QT/QTc study: a single supratherapeutic dose of raltegravir does not prolong the QTcF interval.* J Clin Pharmacol, 2008. **48**: p. 726-33.

20. Chen, S.M., S.S.; Peppercorn, A., et al., *Effect of a single supratherapeutic dose of dolutegravir on cardiac repolarization.* Pharmacotherapy, 2012. **32**: p. 333-9.

21. Lou, Y.B., A.M.; Chen, S., et al., *Effect of Cabotegravir on Cardiac Repolarization in Healthy Subjects.* Clin Pharmacol Drug Dev, 2016. **5**: p. 509-16.

22. Davis, J.D.H., F.; Layton, G., et al. . 2008; 65 Suppl 1: 68-75, *Effect of single doses of maraviroc on the QT/QTc interval in healthy subjects.* Br J Clin Pharmacol, 2008. **65**: p. 68-75.

23. O'Mara, E.K., C.; Huddlestone, J.R., et al., *Effect of Vicriviroc on the QT/Corrected QT Interval and Central Nervous System in Healthy Subjects.* Antimicrob Agents Chemother, 2010. **54**: p. 2448-54.

24. Goldenberg, I.M., A.J.; Zareba, W., *QT interval: how to measure it and what is "normal".* J Cardiovasc Electrophysiol, 2006. **17**: p. 333-6.

25. Postema, P.G.D.J., J.S.; Van der Bilt, I.A., et al., *Accurate electrocardiographic assessment of the QT interval: teach the tangent.* Heart Rhythm, 2008. **5**: p. 1015-8.

26. Vandenberk, B.V., E.; Robyns, T., et al., *Which QT Correction Formulae to Use for QT Monitoring?* J Am Heart Assoc, 2016. **5**: p. 1-10.

27. Walmsley, S.L.A., A.; Clumeck, N., et al., *Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection.* N Engl J Med, 2013. **369**: p. 1807-18.

28. Raffi, F.R., A.; Stellbring, H.J., et al., *Once daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48-week results from the randomised, doubleblind, non-inferiority SPRING-2 study.* Lancet, 2013. **381**: p. 735-43.

29. Patel, D.A.S., S.J.; Tang, W.Y., et al., *48-week efficacy and safety of dolutegravir relative to commonly used third agents in treatment-naïve HIV-1-infected patients: a systematic review and network meta-analysis.* PLoS One, 2014. **9**: p. e105653.

30. Clotet, B.F., J.; Van Lunzen, J., et al., *Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviralnaïve adults with HIV-1 infection (FLAMINGO): 48 week results from randomised open-label phase 3b study.* Lancet, 2014. **383**: p. 2222-31.

APPENDICES

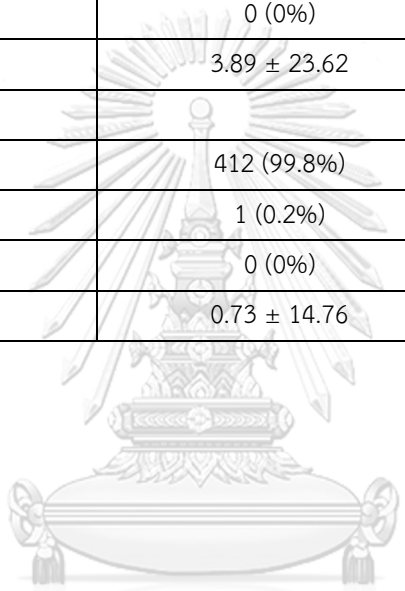
APPENDIX A

Table 6. Demographic data of all patients.

Variables	Statistics data	
	Mean ± SD. or n (%)	Median [min - max]
Age	56.06 ± 5.49	55 [50 - 76]
Gender		
Male	249 (60.3%)	
Female	164 (39.7%)	
Nationality		
Thai	410 (99.3%)	
Other	3 (0.7%)	
Weight	61.13 ± 11.69	60 [36 - 133]
Height	162.37 ± 8.72	163 [134 - 187]
BMI	23.12 ± 3.62	22.86 [15.06 - 43.43]
18.5-24.99	272 (65.9%)	
<18.5	34 (8.2%)	
>=25	107 (25.9%)	
Hypertension	164 (39.7%)	
Diabetes	56 (13.6%)	
Dyslipidemia	290 (70.2%)	
CVA	7 (1.7%)	
Alcohol	71 (17.2%)	
Smoking		
None	298 (72.2%)	
Smoking Currently	59 (14.3%)	
Smoking Previously	56 (13.6%)	
Pack Year		
No	298 (72.2%)	
1-9	43 (10.4%)	
10-19	43 (10.4%)	
>=20	29 (7%)	
Duration of Infection (Month)	234.57 ± 68.34	245 [3 - 386]
CD4 Level	640.46 ± 242.98	607 [72 - 1903]
Viral Load		

Variables	Statistics data	
	Mean ± SD. or n (%)	Median [min - max]
<40	401 (97.1%)	
>=40	12 (2.9%)	
Viral Load Number	2.48 ± 18.51	0 [0 - 283]
CDC Stage		
A	154 (37.3%)	
B	191 (46.2%)	
C	68 (16.5%)	
TDF	284 (68.8%)	
TDF Dose	180.15 ± 133.09	300 [0 - 300]
3TC	225 (54.5%)	
3TC Dose	148.18 ± 142.33	150 [0 - 300]
FTC	179 (43.3%)	
FTC Dose	86.68 ± 99.23	0 [0 - 200]
ABC	70 (16.9%)	
ABC Dose	101.69 ± 225.38	0 [0 - 600]
ZDV	17 (4.1%)	
ZDV Dose	19.85 ± 96.76	0 [0 - 600]
TAF	16 (3.9%)	
TAF Dose	0.97 ± 4.83	0 [0 - 25]
NNRTI		
None	142 (34.4%)	
RPV	152 (36.8%)	
EFV	80 (19.4%)	
NTV	39 (9.4%)	
ETR	0 (0%)	
NNRTI Dose	159.81 ± 238.46	25 [0 - 600]
PI		
None	279 (67.6%)	
ATV	72 (17.4%)	
LPV	53 (12.8%)	
DRV	9 (2.2%)	
SQV	0 (0%)	
PI Dose	141.65 ± 258	0 [0 - 1200]

Variables	Statistics data	
	Mean ± SD. or n (%)	Median [min - max]
RTV	133 (32.2%)	
RTV Dose	39.47 ± 62.06	0 [0 - 200]
II		
None	390 (94.4%)	
RAL	1 (0.2%)	
DTG	21 (5.1%)	
EVG	1 (0.2%)	
CBG	0 (0%)	
II Dose	3.89 ± 23.62	0 [0 - 400]
CCR		
None	412 (99.8%)	
MVC	1 (0.2%)	
VVC	0 (0%)	
CCR Dose	0.73 ± 14.76	0 [0 - 300]



APPENDIX B

Table 7. ECG data of all patients.

Variables	Statistics data	
	Mean ± SD. or n (%)	Median [min - max]
Rhythm		
SR	412 (99.8%)	
AR	0 (0%)	
AF	0 (0%)	
AFL	1 (0.2%)	
Rate	67.24 ± 10.95	66 [40 - 101]
PR Interval	169.56 ± 23.25	168 [101 - 240]
AV Block		
None	372 (90.1%)	
First	41 (9.9%)	
Second	0 (0%)	
Third	0 (0%)	
High-grade	0 (0%)	
QRS Duration	93.31 ± 13.45	93 [58 - 155]
QRS prolongation (yes)	15 (3.6%)	
QRS beyond normal (ms)	7.6 ± 8.94	6 [1 - 35]
QT Interval	413.44 ± 32.19	412 [336 - 543]
QT Intraobserver	409.72 ± 31.12	405.5 [366 - 544]
QT Interobserver	409.54 ± 30.85	407 [366 - 544]
Bazett's Formula	434.4 ± 27.52	434 [352.37 - 531.57]
BAZ QTc prolongation (yes)	96 (23.2%)	
BAZ beyond normal (ms)	15.65 ± 13.61	11.5 [1 - 72]
Fridericia's Formula	426.98 ± 24.21	426.42 [363.24 - 514.37]
FRI QTc prolongation (yes)	52 (12.6%)	
FRI beyond normal (ms)	14.06 ± 13.58	9 [1 - 64]
Framingham's Formula	413.45 ± 32.18	412 [336.04 - 542.97]
FRA QTc prolongation	37 (9%)	
FRA beyond normal (ms)	25.11 ± 22.77	16 [1 - 93]
QTc for analysis		
No	321 (77.7%)	

Variables	Statistics data	
	Mean ± SD. or n (%)	Median [min - max]
Yes	92 (22.3%)	
QTc beyond normal (ms)	14.73 ± 12.83	11 [1 - 72]

APPENDIX C

Case Record Form

ElectroCardioGraphic QT Interval Prolongation in THAI HIV infected Population After Receiving AntiRetroviral Therapy: ECG THAI-HAART Study

ลำดับที่ ☐☐☐ NO

วันที่ทำ ECG ☐☐/☐☐/☐☐☐☐ DATE

Part I.) Personal data

1. อายุ ☐☐ Years old AGE

2. เพศ ☐01 Male ☐02 Female GEND

3. เชื้อชาติ ☐01 Thai ☐02 Other, specify..... NAT

4. น้ำหนัก ☐☐ kg HT

5. ส่วนสูง ☐☐☐ cm WT

6. BMI ☐☐ . ☐☐ kg/m^2 BMI

7. ความเสี่ยงโรคหัวใจและหลอดเลือด RISK

☐01 None ☐02 HT ☐03 DM

☐04 DLP ☐05 CVA ☐06 Alcohol

☐07 Smoking; amount..... มวนต่อวัน, สูบมา..... ปี, หยุดสูบ..... ปี

8. ยาฆ่าเชื้อ ในช่วง 1 เดือนที่ผ่านมา ATB

☐01 Macrolides

(Azithromycin, Clarithromycin, Roxithromycin)

Dose……. mg/day, Duration……. day/week/month/year

☐02 Fluoroquinolones

(Levofloxacin, Ciprofloxacin, Moxifloxacin, Ofloxacin, Norfloxacin)

Dose……. mg/day, Duration……. day/week/month/year

☐03 Co-trimoxazole

(Trimethoprim/Sulfamethoxazole, Bactrim)

Dose……. mg/day, Duration……. day/week/month/year

☐04 Azole

(Fluconazole, Itraconazole, Voriconazole)

Dose……. mg/day, Duration……. day/week/month/year

9. ยารักษาหัวใจเต้นผิดจังหวะ ในช่วง 1 เดือนที่ผ่านมา AAD

☐01 Class IC

(Flecainide)

Dose……. mg/day, Duration……. day/week/month/year

☐02 Class III

(Amiodarone, Sotalol)

Dose……. mg/day, Duration……. day/week/month/year

10. ยาจิตเวช ในช่วง 1 เดือนที่ผ่านมา APD

☐01 Typical

(Haloperidol)

Dose……. mg/day, Duration……. day/week/month/year

☐02 Atypical

(Risperidone, Clozapine, Quetiapine)

Dose……. mg/day, Duration……. day/week/month/year

Part II.) Disease data

1. ระยะเวลาติดเชื้อ ☐☐ day/week/month/year DUR

2. $CD4^+$ count ☐☐☐☐cells/mcl CD4

3. Viral load ……. copies/ml VL

4. HIV stage ☐ STAGE

Part III.) Management data:

1. Types of Antiretroviral therapy

☐01 None

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

☐02 Zidovudine (AZT, ZDV)

Dose……. mg/day, Duration……. day/week/month/year

☐03 Lamivudine (3TC)

Dose……. mg/day, Duration……. day/week/month/year

☐04 Didanosine (ddl)

Dose……. mg/day, Duration……. day/week/month/year

☐05 Stavudine (d4T)

Dose……. mg/day, Duration……. day/week/month/year

☐06 Abacavir (ABC)

Dose……. mg/day, Duration……. day/week/month/year

☐07 Tenofovir (TDF)

Dose……. mg/day, Duration……. day/week/month/year

☐08 Emtricitabine (FTC)

Dose……. mg/day, Duration……. day/week/month/year

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

☐09 Efavirenz (EFV)

Dose……. mg/day, Duration……. day/week/month/year

☐10 Etravirine (ETR)

Dose……. mg/day, Duration……. day/week/month/year

☐11 Nevirapine (NVP)

Dose……. mg/day, Duration……. day/week/month/year

☐12 Rilpiverine (RPV)

Dose……. mg/day, Duration……. day/week/month/year

Protease Inhibitors (PIs)

☐13 Atazanavir (ATV)

Dose……. mg/day, Duration……. day/week/month/year

☐14 Ritonavir (RTV)

Dose……. mg/day, Duration……. day/week/month/year

☐15 Lopinavir (LPV)

Dose……. mg/day, Duration……. day/week/month/year

☐16 Darunavir (DRV)

Dose……. mg/day, Duration……. day/week/month/year

☐17 Saquinavir (SQV)

Dose……. mg/day, Duration……. day/week/month/year

Integrase Inhibitor (PIs)

☐18 Raltegravir (RAL)

Dose……. mg/day, Duration……. day/week/month/year

☐19 Elvitegravir (EVG)

Dose……. mg/day, Duration……. day/week/month/year

☐20 Dolutegravir (DTG)

Dose……. mg/day, Duration……. day/week/month/year

☐21 Cabotegravir (S/GSK1265744 or GSK744)

Dose……. mg/day, Duration……. day/week/month/year

CCR5 co-receptor antagonist

☐22 Maraviroc (MVC)

Dose……. mg/day, Duration……. day/week/month/year

☐23 Vicriviroc (MVC)

Dose……. mg/day, Duration……. day/week/month/year

Part IV.) ECG data:

1. Rhythm RHYTH

☐01 Sinus rhythm ☐02 Atrial rhythm

☐03 Junctional rhythm ☐04 Ventricular rhythm

☐05 Atrial flutter ☐06 Atrial fibrillation

☐07 Other, specify.....

2. AV block BLOCK

☐01 First degree ☐02 Second degree

3. Rate ☐☐☐ bpm RATE

4. QTc interval ☐☐☐ milliseconds QTC

5. QRS duration ☐☐☐ milliseconds QRS

6. PR interval ☐☐☐ milliseconds PR

VITA

NAME	Nonthikorn Theerasuwipakorn
DATE OF BIRTH	6 March 1990
PLACE OF BIRTH	Bangkok, Thailand
INSTITUTIONS ATTENDED	2008 – 2013 Doctor of Medicine Program, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand 2013 – 2014 Internship, Rayong Hospital 2014 – 2018 Resident training, Department of Internal Medicine, King Chulalongkorn Memorial Hospital 2018 - 2020 Cardiology fellowship, Department of Internal Medicine, King Chulalongkorn Memorial Hospital
HOME ADDRESS	92/1 Srinakarin road, Samutprakarn, Thailand 10270
PUBLICATION	Theerasuwipakorn, N.; Tasneem, A.A.; Kongkam, P., et al. Walled-off Peripancreatic Fluid Collections in Asian Population: Paradigm Shift from Surgical and Percutaneous to Endoscopic Drainage. J Transl Int Med. 2019 Dec; 7(4): 170–177.