Published in final edited form as:

J Electrocardiol. 2014 ; 47(2): 264–271. doi:10.1016/j.jelectrocard.2013.12.001.

Determinants of developing widened spatial QRS-T angle in HIV-infected individuals: Results from the Strategies for Management of Antiretroviral Therapy [SMART] Study

Farah Z. Dawood, MD^a, Mollie P. Roediger, MS^b, Greg Grandits, MS^b, Dery Miller, BS^c, Martin Fisher, MD^d, Zhu-Ming Zhang, MD^e, Sally Hodder, MD^f, Jennifer F. Hoy, MD^g, Jens D. Lundgren, MD^h, James D. Neaton, PhD^b, Elsayed Z. Soliman, MD, MSc, MS^{a,e}, and Group INSIGHT SMART Study

^aDepartment of Internal Medicine, Secion on Cardiology, Wake Forest School of Medicine, Winston Salem, NC, USA

^bDivision of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN, USA

^cSchool of Medicine, Wake Forest Health Sciences, Winston Salem, NC, USA

^dBrighton and Sussex University Hospitals NHS Trust, Brighton, UK

^eEpidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine, Winston Salem, NC, USA

^fDepartment of Medicine, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, NJ, USA

^gInfectious Diseases Department, The Alfred Hospital and Monash University, Melbourne, Australia

^hCopenhagen HIV Program (CHIP), State University Hospital and University of Copenhagen, Copenhagen, Denmark

Abstract

Background—A widened electrocardiographic spatial QRS-T angle has been shown to be predictive of cardiovascular disease in HIV-infected individuals. However, determinants and risk factors of developing widened QRS-T angle over time in this population remain unknown.

Methods and Results—Spatial QRS-T angle was automatically measured from standard electrocardiogram of 1444 HIV-infected individuals without baseline widened spatial QRS-T angle from the Strategies for Management of Antiretroviral Therapy [SMART], a clinical trial comparing two antiretroviral treatment strategies [Drug Conservation (DC) vs. Viral Suppression (VS)]. Conditional logistic regression analysis was used to examine the association between baseline characteristics and incident widened spatial QRS-T angle (a new angle ≥ 93 degrees in males and ≥ 74 degrees in females). During 2544 person-years of follow-up, 199 participants

© 2013 Elsevier Inc. All rights reserved.

Correspondence: Elsayed Z. Soliman MD, MSc, MS, FAHA, FACC, Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine, Medical Center Blvd, Winston Salem, NC 27157, Phone: (336) 716-8632 Fax: (336) 716-0834, esoliman@wakehealth.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosures: None

developed widened angle at a rate of 7.8 per 100 person-years. In unadjusted models, female sex, black race (vs. white), DC treatment strategy, current and past smokers (vs. never), history of alcohol abuse, greater body mass index, history of diabetes and higher levels of hs-C-reactive protein were associated with incident widened spatial QRS-T angle. When these variables entered together in the same model with adjustment for demographics and treatment strategy, DC treatment strategy [OR (95% CI): 1.50 (1.09, 2.07)], female gender [1.69 (1.17, 2.45)], current and past smoking (vs. never) [2.49 (1.63, 3.81) and 1.93 (1.21, 3.09), respectively], and diabetes [2.28 (1.33, 3.91)] predicted incident widened spatial QRS-T angle.

Conclusions—Drug conservation treatment strategy, female gender, smoking, and diabetes are independently predictive of incident widened spatial QRS-T angle in HIV-infected individuals.

Keywords

Spatial QRS-T angle; Electrocardiogram; cardiovascular disease; HIV/AIDS

INTRODUCTION

The spatial QRS-T angle, defined as the angle between the mean QRS and T vector in the 12-lead electrocardiogram (ECG), has been shown to be associated with incident cardiovascular disease (CVD) and total mortality in the general population [1–6]. We recently showed that widened spatial QRS-T angle at study entry of the Strategies for Management of Antiretroviral Therapy (SMART) trial was predictive of CVD events in HIV-infected individuals [7]. However, risk factors and determinants of developing widened QRS-T angle over time in this population remain unknown. Filling this gap in the current knowledge will expand our understanding of the dynamicity of spatial QRS-T angle during HIV-disease course as it relates to the antiretroviral treatment strategy studied in SMART and baseline characteristics. This subsequently can help identifying HIV-infected individuals at increased risk of CVD events. We sought to determine the clinical correlates and baseline characteristics associated with widening of spatial QRS-T angle over time in the SMART study. With its standardized ascertainment of the disease status, treatment status and clinical variables including high-quality digital 12-lead ECG, SMART trial is uniquely suited to address this topic.

METHODS

Detailed descriptions of the design and aims of the SMART trial have been published elsewhere [8–9]. Briefly, SMART was an open-label, randomized trial comparing two antiretroviral treatment (ART) strategies: Viral Suppression strategy (VS), the control arm, was defined to be consistent with the guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents [10]; that is, antiretroviral regimens were to be used in an uninterrupted manner with the goal of maximal and continuous suppression of HIV replication. The experimental Drug Conservation (DC) strategy entailed the episodic use of ART according to CD4+ (Cluster Differentiation 4) count thresholds; that is, the use of ART was deferred until the CD4+ count decreased to less than 250 cells per cubic millimeter (cells/mm³), at which time ART was to be initiated (or reinitiated) and continued until the CD4+ count increased to more than 350 cells/mm³. On January, 2006, the data and safety monitoring board recommended stopping enrollment in the SMART trial because of a safety risk in the DC group. Subsequently, the protocol was modified, all patients were advised to receive continuous ART, and follow-up continued for an additional 1.5 years. This analysis describes findings through the protocol change on January, 2006.

SMART recruited individuals infected with HIV who were older than 13 years and were not pregnant or breast-feeding. Subjects were eligible for inclusion in SMART if their CD4+

count exceeded 350 cells/mm³ and they were willing to participate. All participants in the trial were considered eligible for the present analysis except those with missing or poor-quality baseline ECG data (n = 646) or with ECG conditions that interfere with calculation of spatial QRS-T angle (n=79) as well as participants who were randomized in the year before protocol changes and did not have chance to have any annual follow up visits prior to January 2006 (n = 2753). After all exclusions, 1444 participants (727 in the DC arm and 717 in the VS arm) were included in this analysis (Figure 1).

Before randomization (baseline), ART and medical history were obtained, CD4+ count and HIV RNA levels were measured, and a 12-lead ECG was obtained. Follow-up visits were scheduled monthly for the first 2 months, every 2 months thereafter for the first year, and every 4 months in the second and subsequent years. At each visit, a history was taken, an examination was conducted and the CD4+ count and HIV RNA levels were measured. Interleukin-6 (IL-6) and high sensitivity C-reactive protein (hs-CRP) were centrally determined on stored plasma at the end of the study.

At the baseline visit and at each annual visit, a 12-lead ECG was obtained. Detailed description of ECG recording in SMART has been published elsewhere [11]. Briefly, identical electrocardiographs [GE MAC 1200 models, GE Milwaukee, WI] were used in all of the study clinical sites, and standard 12-lead ECGs were recorded in all participants by strictly standardized procedures. The digital ECG tracings stored in the electrocardiographs were transmitted regularly over analog phone lines to the SMART ECG Reading Center, EPICARE, located at Wake Forest School of Medicine, Winston-Salem, NC for analysis. ECGs were evaluated by readers blinded to treatment strategy and ART use. After being visually checked for quality, the study ECGs were automatically processed using the 2001 version of the GE Marquette 12-SL program (GE, Milwaukee, WI). ECG abnormalities were classified using the standard Minnesota ECG Classification [12]. According to Minnesota ECG Classification major ECG abnormalities include major ventricular conduction defect; definite myocardial infarction (defined as the presence of major Q wave abnormalities); possible myocardial infarction (defined as the presence of minor Q/-QS wave plus major ST/-T abnormalities); major isolated -ST/-T abnormalities; left ventricular hypertrophy; major atrioventricular conduction abnormalities; major QT prolongation (QT 116%), pacemaker, and other major arrhythmias. On the other hand, minor ECG abnormalities include minor isolated Q/-QS waves; minor isolated ST/-T abnormalities; high R waves; ST segment elevation; incomplete (left and right) bundle branch block; minor QT prolongation (QTi 112%); short PR interval; left axis deviation; right axis deviation; frequent ventricular premature beats; and other minor miscellaneous abnormalities. For the purpose of this report, the remaining major and minor abnormalities after the exclusions were combined into one group labeled as “any ECG abnormality”. Spatial QRS-T angle was defined the spatial angle between the mean QRS and the mean T vectors.. Mean spatial QRS and T vectors were automatically calculated from quasiorthogonal X, Y, and Z leads reconstructed from standard ECG leads using matrix transformation method [13]. Due to the reported gender differences in its distribution [14], widened spatial QRS-T angle was defined using gender-specific cut points (QRS-T angle > 93 degree in males and > 74 degree in females). These cut points showed the strongest association with incident CVD in HIV-infected individuals [7]. Incident widened QRS-T spatial was defined as developing widened spatial QRS-T during follow up in individuals free of this abnormality at baseline.

Baseline characteristics of the study participants with normal spatial QRS-T angle at baseline were tabulated using mean (SD) for continuous variables and number (%) for categorical variables.

The number of annual ECG assessments varied among the participants due to enrollment over several years [712 participants with 1 follow-up ECG after baseline, 433 with 2 follow-up ECGs, 284 with 3 follow-up ECGs and only 15 with 4 follow-up ECGs]. Therefore, we used conditional logistic regression models stratified by the number of ECG assessments to examine the association between baseline characteristics and incident widened QRS-T angle. In addition to categorical change from normal to widened QRS-T angle, we also examined change in spatial QRS-T angle as a continuous variable over time using longitudinal linear mixed-effects models with a random intercept for each participant. Included in analysis were all follow-up ECGs obtained prior to the protocol change on January 2006.

Initially, univariate models were used to examine the association between each of the baseline characteristics with incident widened spatial QRS-T angle or change in spatial QRS-T angle. Variables with significant associations in the univariate models were then entered together in a multivariable model along with treatment strategy and demographics. Interaction between treatment arm or gender and each of the variables in the final models was examined. Follow-up time was measured from baseline to incident widened spatial QRS-T angle or to the last ECG measurement obtained prior to the protocol change on January 2006. All reported p values are two sided, and $p < .05$ was considered statistically significant. SAS, version 9.1 (SAS Institute, Inc, Cary, NC) was used in all analyses.

RESULTS

The present analysis included 1,444 HIV-infected individuals with normal spatial QRS-T angle at the time of enrollment in the SMART trial (mean age 44 years, 727 in the DC group, 54% non-whites and 27% women). Table 1 shows the baseline characteristics of the participants. Participant characteristics were comparable in the two treatment arms, except for more females in the VS arm ($p=0.02$) and slightly higher total cholesterol in the DC arm ($p=0.04$), data not shown.

The mean (SD) of the spatial QRS-T angle at baseline was 58.9 (19.9) degrees. During 2544 person-years of follow-up, 199 participants developed incident widened QRS-T angle at a rate of 7.8 per 100 person-years.

Table 2 shows the results of the univariate and multivariable adjusted conditional logistic regression analysis for the association between baseline characteristics and incident widened spatial QRS-T angle. As shown, in unadjusted models, female sex, black race (vs. white), assignment to the DC treatment arm, current and past smokers (vs. never), history of alcoholism or alcohol abuse, greater body mass index (BMI), history of diabetes and higher levels of C-reactive protein were associated with incident widened spatial QRS-T angle. When these variables entered together in the same model with adjustment for demographics and treatment arm, DC treatment arm (vs. VS treatment arm) [$p=0.01$], female gender [$p<0.01$], current and past smoking (vs. never) [$p<0.01$ for each] and diabetes [$p<0.01$] predicted incident widened spatial QRS-T angle. There was no significant interaction between each of the variables in the final model and SMART trial arms or gender for incident widened spatial QRS-T angle. Figure 2 shows the differences in incident widened QRS-T angle between treatment arms (VS and DC) in each year stratified by the number of ECGs.

Table 3 shows the results of the association between baseline characteristics with change in spatial QRS-T angle overtime. As shown, DC treatment arm, black race and higher BMI were associated with increase (i.e. more widening) in spatial QRS-T angle over time. On the

other hand, use of lipid lowering drugs was associated with decrease (less widening) in the spatial QRS-T angle.

DISCUSSION

In a previous report from the SMART trial, we showed that widened spatial QRS-T angle is a strong predictor of incident CVD in the HIV-infected individuals [7]. In this analysis, we investigated the risk factors and determinants of developing widened QRS-T angle in the same population. We used two approaches to detect widening spatial QRS-T angle over time. First, we used the shift from a normal QRS-T angle at baseline to an abnormally wide QRS-T angle during follow up (referred to in this discussion as categorical incident analysis) using cut points that have been associated with increased CVD risk. Second, we used change in the levels of spatial QRS-T angle as a continuous variable over time (referred to in this discussion as linear change analysis). While categorical incident analysis provides a simple way to determine factors that result in shift from normal to abnormal (which is more clinically applicable), it leaves chance for not detecting significant changes that might not be large enough to cross the cut-point. Therefore, we decided to use linear change analysis as well, which provides a chance to look at factors that result in change over time in a linear fashion, and subsequently any subtle changes even if not crossing the cut-points of abnormality will be detected. The caveat, however, is that it is not well established that such a linear change is equally predictive of CVD events as the categorical changes for abnormal to normal. In our previous report from SMART study, there were no statistically significant differences in the risk of CVD among the first three quartiles of spatial QRS-T angle, and only the fourth quartile was associated with higher risk. Nevertheless, using both approaches provide a better opportunity to understand the overall factors that determine widening of spatial QRS-T angle.

Results from the multivariable categorical incident analysis show that smoking status (current or past), and diabetes, both linked to CVD risk in the general population, are linked to the development of widened spatial QRS-T angle over time in HIV. Higher BMI, black race and higher levels of hs-CRP, all linked as well to CVD risk in the general population, were associated with incident widened spatial QRS-T in the univariate but not in the multivariable categorical incident analysis. This is probably because the CVD risk associated with these risk factors is through developing other risk factors such as diabetes.

Female gender was associated with higher risk of widened QRS-T angle in the multivariable categorical incident analysis but not in the linear change analysis, and age was not significant in any of the models. These findings are counter intuitive to the known higher risk of CVD in males and older individuals in the general population. The lower cut-point for abnormal spatial QRS-T angle in females and the overall younger age of SMART participants might be playing a role in explaining some of these results. Noteworthy, in a previous report from SMART, there was no significant difference between men and women in the risk of CVD events (15) which accords with our linear change analysis. Further, the association of female gender with the development of ECG abnormalities (as categorical variable) has been previously reported in the general population. In the Women's Health Initiative (WHI) trial, increased prevalence of ECG abnormalities was demonstrated and was independently associated with CVD events [16]. Further, spatial QRS-T angle has been shown to be a strong predictor of incident CVD in women with a 114% increased risk in the atherosclerosis risk in communities study (ARIC) [17].

In the univariate and multivariable categorical incident analysis as well as linear change analysis drug conservation strategy (compared to viral suppression strategy) was associated with widening of spatial QRS-T angle. These findings are consistent with previous reports

that intermittent ART use leads to detrimental outcome in this population partially due to increased CVD events (8). In a previous report from the SMART trial, the drug conservation strategy was associated with lower CD4 count and excess risk of CVD events during follow up (15).

Taken together, our findings show that HIV treatment strategy and several of the known CVD risk factors are linked to widening of spatial QRS-T angle, which in turn has been shown to be a predictor of CVD events. Hence, spatial QRS-T angle could be used as a “monitoring” tool to examine progression of the CVD risk in HIV-infected individuals from the stage of having risk factors to the stage of occurrence of actual CVD events. Our findings along with results of previous reports [11] highlight the potential usefulness of routine ECG as a tool for CVD risk stratification in the HIV population. Noteworthy, in general QRS-T angle can be widened with altered spatial direction of the QRS vector due to altered depolarization, structural changes, old myocardial infarction, slowed conduction or fascicular blocks, and associated secondary repolarization abnormalities, and change in spatial direction of T vectors. The second major mechanism for widened QRS/T is the presence of primary repolarization abnormalities. Since we excluded individuals with QRS duration ≥ 120 ms, the observed widening of QRS/T angle was more likely due to primary repolarization abnormalities than abnormal depolarization.

In this era of effective ART, the increase in survival of HIV infected individuals has been associated with fewer AIDS-related deaths [18]. On the other hand, CVD is emerging as a significant contributor to mortality accounting for 8%–22% of deaths among HIV-infected individuals, and the percentage appears to be increasing as the HIV-infected population ages [19–23]. A number of studies have shown that there is an increased risk of CVD in HIV-infected populations compared to uninfected populations [24–29], although some of the comparisons could not control for known differences such as smoking and other CVD risk factors. This implies that there could be unique additional CVD risk factors in the setting of HIV that makes HIV-infected individuals at a higher risk for CVD; which calls for better understanding of CVD risk factors in the HIV population (30). In this context, established CVD risk factors in the general population probably “works” in HIV – but they may be modified by the underlying HIV infection or some of the drugs used to treat HIV. Hence, not surprisingly to see that CVD screening guidelines and risk scores in HIV infected individuals shadow those for the general population [31–35]. An intermediate link between the CVD risk factors and actual CVD events such as spatial QRS-T angle could play a role in developing new risk stratification scores targeting HIV-infected individuals.

The prevalence of cigarette smoking among HIV-infected individuals is notably higher than in the general population [36–37]. Previous studies have suggested that smoking may negatively modify CD4+ lymphocyte count in individuals infected with HIV on ART [38]. We have shown that smoking, past or current, is directly related to increased incidence of widened spatial QRS-T angle. It may be reasonable to speculate that smoking cessation in HIV population could be one of the key strategies for improvement in global CVD risk and anticipated improvement in survival in a way similar to or even better than it is in the general population. Along the same lines, obesity has been shown to be associated with a wide variety of ECG abnormalities mostly related to alteration in cardiac morphology including change in the axis of QRS and T angle which can be reversible with weight loss [39]. Therefore, obesity could be another modifiable CVD risk factor that can lead to improved survival in HIV infected individuals.

Limitations

Our results should be read in the context of certain limitations. This analysis was conducted on individuals who chose to enter a clinical trial of HIV treatment. Thus, it is possible that

the results are not generalizable to all HIV-infected individuals. Nevertheless, this analysis was conducted on a well-defined population of HIV-infected patients from different races/ethnicities with reasonable representation of women.

We used blood pressure lowering drugs as surrogate for hypertension since SMART trial did not collect blood pressure data at the baseline. Also, there was no data on cocaine use which could cause myocardial injury. Nevertheless, all other variables included in this analysis were carefully collected and ascertained including the ECG data which was obtained by trained technicians using a standardized protocol.

Conclusions

Drug conservation treatment strategy, female gender, smoking, and diabetes are independently predictive of incident widened spatial QRS-T angle in HIV-infected individuals. Given the previously reported link between increased cardiovascular risk and widened spatial QRS-T angle in HIV-infected individuals, these findings contribute to our understanding of the process of developing cardiovascular disease in HIV which could have implication in disease prevention and risk stratification.

Acknowledgments

We thank the SMART study investigators and participants. For a complete list of SMART investigators, see *N Engl J Med* 2006;355: 2283–2296.

Funding source: The SMART study was sponsored by the National Institute of Allergy and Infectious Disease, National Institutes of Health (grants U01AI042170, U01AI046362, and U01AI068641).

References

1. Kors JA, Kardys I, van der Meer IM, van Herpen G, Hofman A, van der Kuip DA, Witteman JC. Spatial QRS-T angle as a risk indicator of cardiac death in an elderly population. *J Electrocardiol.* 2003; 36:113–114. [PubMed: 14716610]
2. Kardys I, Kors JA, van der Meer IM, Hofman A, van der Kuip DA, Witteman JC. Spatial QRS/T angle predicts cardiac death in a general population. *Eur Heart J.* 2003; 24:1357–1364. [PubMed: 12871693]
3. de Torbal A, Kors JA, van Herpen G, Meij S, Nelwan S, Simoons ML, Boersma E. The electrical T-axis and the spatial QRS-T angle are independent predictors of long-term mortality in patients admitted with acute ischemic chest pain. *Cardiol.* 2004; 101:199–207.
4. Rautaharju PM, Ge S, Nelson JC, Marino Larsen EK, Psaty BM, Furberg CD, Zhang ZM, Robbins J, Gottdiener JS, Chaves PH. Comparison of mortality risk for electrocardiographic abnormalities in men and women with and without coronary heart disease (from the Cardiovascular Health Study). *Am J Cardiol.* 2006; 97:309–315. [PubMed: 16442387]
5. Whang W, Shimbo D, Levitan EB, Newman JD, Rautaharju PM, Davidson KW, Muntner P. Relations between QRS/T angle, cardiac risk factors, and mortality in the third National Health and Nutrition Examination Survey (NHANES III). *Am J Cardiol.* 2012; 109(7):981–7. [PubMed: 22221946]
6. Yamazaki T, Froelicher VF, Myers J, Chun S, Wang P. Spatial QRS-T angle predicts cardiac death in a clinical population. *Heart Rhythm.* 2005; 2:73–78. [PubMed: 15851268]
7. Dawood FZ, Khan F, Roediger MP, Zhang ZM, Swaminathan S, Klinker H, Hoy J, Lundgren JD, Neaton JD, Soliman EZ, INSIGHT SMART Study Group. Electrocardiographic spatial QRS-T angle and incident cardiovascular disease in HIV-infected patients (from the Strategies for the Management of Antiretroviral Therapy [SMART] study). *Am J Cardiol.* 2013; 111(1):118–24. [PubMed: 23062314]
8. The SMART Study Group. CD4+ count-guided interruption of antiretroviral therapy. *N Engl J Med.* 2006; 355:2283–2296. [PubMed: 17135583]

9. SMART Study Group. Risk for opportunistic disease and death after reinitiating continuous antiretroviral therapy in patients with HIV previously receiving episodic therapy, a randomized trial. *Ann Intern Med.* 2008; 149:289–299. [PubMed: 18765698]
10. Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at: <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>. Accessed March 13, 2012
11. Soliman EZ, Prineas RJ, Roediger MP, Duprez DA, Boccara F, Boesecke C, Stephan C, Hodder S, Stein JH, Lundgren JD, Neaton JD. Prevalence and prognostic significance of ECG abnormalities in HIV-infected patients: results from the Strategies for Management of Antiretroviral Therapy study. *J Electrocardiol.* 2011; 44:779–785. [PubMed: 21145066]
12. Prineas, RJ.; Crow, RS.; Blackburn, H. The Minnesota Code Manual of Electrocardiographic Findings. Boston: John Wright PSG Inc; 1982. p. 223–229.
13. Edenbrandt L, Pahlm O. Vector cardiogram synthesized from a 12-lead ECG: superiority of the inverse Dower matrix. *J Electrocardiol.* 1988; 21:361–367. [PubMed: 3241148]
14. Schreurs CA, Algra AM, Man SC, Cannegieter SC, van der Wall EE, Schalij MJ, Kors JA, Swenne CA. The spatial QRS-T angle in the Frank vectorcardiogram: accuracy of estimates derived from the 12-lead electrocardiogram. *J Electrocardiol.* 2010; 43:294–301. [PubMed: 20417936]
15. Phillips AN, Carr A, Neuhaus J, Visnegarwala F, Prineas R, Burman WJ, Williams I, Drummond F, Duprez D, Belloso WH, Goebel FD, Grund B, Hatzakis A, Vera J, Lundgren JD. Interruption of antiretroviral therapy and risk of cardiovascular disease in persons with HIV-1 infection: exploratory analyses from the SMART trial. *Antivir Ther.* 2008; 13(2):177–87. [PubMed: 18505169]
16. Denes P, Larson JC, Lloyd-Jones DM, Prineas RJ, Greenland P. Major and minor ECG abnormalities in asymptomatic women and risk of cardiovascular events and mortality. *JAMA.* 2007; 297(9):978–985. [PubMed: 17341712]
17. Zhang ZM, Prineas RJ, Case D, Soliman EZ, Rautaharju PM, ARIC Research Group. Comparison of the prognostic significance of the electrocardiographic QRS/T angles in predicting incident coronary heart disease and total mortality (from the Atherosclerosis Risk in Communities Study). *Am J Cardiol.* 2007; 100(5):844–849. [PubMed: 17719331]
18. Bedimo RJ, Westfall AO, Drechsler H, Vidiella G, Tebas P. Abacavir use and risk of acute myocardial infarction and cerebrovascular events in the highly active antiretroviral therapy era. *Clin Infect Dis.* 2011; 53(1):84–91. [PubMed: 21653308]
19. Lewden C, Salmon D, Morlat P, Bévilacqua S, Jougla E, Bonnet F, Héripert L, Costagliola D, May T, Chêne G, Mortality 2000 study group. Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS. *Int J Epidemiol.* 2005; 34:121–30. [PubMed: 15561752]
20. Lewden C, May T, Rosenthal E, Burty C, Bonnet F, Costagliola D, Jougla E, Semaille C, Morlat P, Salmon D, Cacoub P, Chêne G, ANRS EN19 Mortalité Study Group and Mortaviv1. Changes in causes of death among adults infected by HIV between 2000 and 2005: The “Mortalite 2000 and 2005” surveys (ANRS EN19 and Mortaviv). *J Acquir Immune Defic Syndr.* 2008; 48:590–8. [PubMed: 18645512]
21. Crum NF, Riffenburgh RH, Wegner S, Agan BK, Tasker SA, Spooner KM, Armstrong AW, Fraser S, Wallace MR, Triservice AIDS Clinical Consortium. Comparisons of causes of death and mortality rates among HIV-infected persons: analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. *J Acquir Immune Defic Syndr.* 2006; 41:194–200. [PubMed: 16394852]
22. Smith, C.; Group DADS. Association between modifiable and nonmodifiable risk factors and specific causes of death in the HAART Era: the data collection on adverse events of anti-HIV drugs study [abstract 145]; Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections; Montreal, Canada. 2009.
23. Luther VP, Wilkin AM. HIV infection in older adults. *Clin Geriatr Med.* 2007; 23:567–83. vii. [PubMed: 17631234]
24. Currier JS, Taylor A, Boyd F, Dezii CM, Kawabata H, Burtcel B, Maa JF, Hodder S. Coronary heart disease in HIV-infected individuals. *J Acquir Immune Defic Syndr.* 2003; 33:506–512. [PubMed: 12869840]

25. Friis-Møller N, Sabin CA, Weber R, d'Arminio Monforte A, El-Sadr WM, Reiss P, Thiébaud R, Morfeldt L, De Wit S, Pradier C, Calvo G, Law MG, Kirk O, Phillips AN, Lundgren JD, Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med*. 2003; 349:1993–2003. [PubMed: 14627784]
26. Friis-Møller N, Reiss P, Sabin CA, Weber R, Monforte A, El-Sadr W, Thiébaud R, De Wit S, Kirk O, Fontas E, Law MG, Phillips A, Lundgren JD, DAD Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007; 356:1723–1735. [PubMed: 17460226]
27. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab*. 2007; 92:2506–2512. [PubMed: 17456578]
28. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. *N Engl J Med*. 2003; 348:702–710. [PubMed: 12594314]
29. Lang S, Mary-Krause M, Cotte L, Gilquin J, Partisani M, Simon A, Boccara F, Bingham A, Costagliola D, French Hospital Database on HIV-ANRS CO4. Increased risk of myocardial infarction in HIV-infected patients in France, relative to the general population. *AIDS*. 2010; 24:1228–30. [PubMed: 20400883]
30. Boccara F, Lang S, Meuleman C, Ederhy S, Mary-Krause M, Costagliola D, Capeau J, Cohen A. HIV and Coronary heart disease: time for a better understanding. *J Am Coll Cardiol*. 2013; 61(5): 511–23. [PubMed: 23369416]
31. Dube MP, Stein JH, Aberg JA, Fichtenbaum CJ, Gerber JG, Tashima KT, Henry WK, Currier JS, Sprecher D, Glesby MJ, Adult AIDS Clinical Trials Group Cardiovascular Subcommittee; HIV Medical Association of the Infectious Disease Society of America. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis*. 2003; 37:613–27. [PubMed: 12942391]
32. Grinspoon SK, Grunfeld C, Kotler DP, Currier JS, Lundgren JD, Dubé MP, Lipshultz SE, Hsue PY, Squires K, Schambelan M, Wilson PW, Yarasheski KE, Hadigan CM, Stein JH, Eckel RH. State of the science conference: Initiative to decrease cardiovascular risk and increase quality of care for patients living with HIV/AIDS: executive summary. *Circulation*. 2008; 118:198–210. [PubMed: 18566320]
33. Lundgren JD, Battegay M, Behrens G, De Wit S, Guaraldi G, Katlama C, Martinez E, Nair D, Powderly WG, Reiss P, Sutinen J, Vigano A, EACS Executive Committee. European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV. *HIV Med*. 2008; 9:72–81. [PubMed: 18257770]
34. Law MG, Friis-Møller N, El-Sadr WM, Weber R, Reiss P, D'Arminio Monforte A, Thiébaud R, Morfeldt L, De Wit S, Pradier C, Calvo G, Kirk O, Sabin CA, Phillips AN, Lundgren JD, D:A:D Study Group. The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D Study. *HIV Med*. 2006 May; 7(4):218–30. [PubMed: 16630034]
35. Friis-Møller N, Thiébaud R, Reiss P, Weber R, Monforte AD, De Wit S, El-Sadr W, Fontas E, Worm S, Kirk O, Phillips A, Sabin CA, Lundgren JD, Law MG, DAD study group. Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. *Eur J Cardiovasc Prev Rehabil*. 2010 Oct; 17(5):491–501. [PubMed: 20543702]
36. Royce RA, Winkelstein W Jr. HIV infection, cigarette smoking and CD41 T-lymphocyte counts: preliminary results from the San Francisco men's health study. *AIDS*. 1990; 4:327–333. [PubMed: 1972021]
37. Friis-Møller N, Weber R, Reiss P, Thiébaud R, Kirk O, d'Arminio Monforte A, Pradier C, Morfeldt L, Mateu S, Law M, El-Sadr W, De Wit S, Sabin CA, Phillips AN, Lundgren JD, DAD Study Group. Cardiovascular disease risk factors in HIV patients: association with antiretroviral therapy: results from the DAD study. *AIDS*. 2003; 17:1179–1193. [PubMed: 12819520]

38. Park LP, Margolick JB, Giorgi JV, Ferbas J, Bauer K, Kaslow R, Munoz A. Influence of HIV-1 infection and cigarette smoking on leukocyte profiles in homosexual men: The Multicenter AIDS Cohort Study. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1992; 5:1124–1130.
39. Fraley MA, Birchem JA, Senkottaiyan N, Alpert MA. Obesity and the electrocardiogram. *Obes Rev.* 2005; (4):275–281. [PubMed: 16246213]

Figure 1.
Flow diagram of exclusion and inclusion criteria

Figure 2.
Incident widened spatial QRS-T angle by treatment arm and number of electrocardiograms

Table 1

Baseline characteristics

Characteristic	N (%) or mean (SD)
Age (in years)	44.1 (9.2)
Gender (% female)	384 (26.6%)
Race	
Black	543 (37.6%)
White	671 (46.5%)
Asian	14 (1.0%)
Other	216 (15.0%)
Smoking	
Current	614 (42.5%)
Former	364 (25.2%)
Never	466 (32.3%)
History of alcoholism/alcohol abuse (%)	233 (16.1%)
Total Cholesterol (mg/dl)	193.8 (49.3)
LDL- Cholesterol (mg/dl)	110.4 (34.4)
HDL- Cholesterol (mg/dl)	43.6 (15.0)
Triglycerides (mg/dl)	227.7 (221.8)
Total cholesterol/HDL	5.0 (2.7)
High sensitivity C reactive protein (µg/ml)	3.8 (6.3)
Interleukin-6 (pg/ml)	2.8 (3.6)
Body mass index (kg/m ²)	26.5 (5.4)
Diabetes mellitus	95 (6.6%)
Blood pressure lowering drugs	288 (19.9%)
Lipid lowering drugs	238 (16.5%)
Hepatitis B or C	289 (20.2%)
Baseline CD4 count (cells/mm ³)	656.5 (249.7)
HIV RNA (% > 400 copies/mL)	886 (61.5%)
Baseline HIV-RNA and antiretroviral (ART) Status	
Off ART	295 (20.5%)
On ART, HIV-RNA < 400	298 (20.7%)
On ART, HIV-RNA > 400	848 (58.8%)
QRS-T spatial angle	58.9 (19.9)
Any ECG abnormalities	701 (48.5%)
Prior cardiovascular disease	77 (5.3%)

Table 2

Baseline predictors of incident widened spatial QRS-T angle* using conditional logistic regression analysis

	Univariate Models		Multivariable Model [†]	
	OR [95% CI]	P	OR [95% CI]	P
Treatment Group (DC vs. VS)	1.38 (1.02, 1.88)	0.04	1.50 (1.09, 2.07)	0.01
Age (year)	1.00 (0.99, 1.02)	0.85	0.99 (0.98, 1.01)	0.53
Gender (Female vs. Male)	1.81 (1.31, 2.48)	<0.001	1.69 (1.17, 2.45)	0.005
Race				
Black (vs. White)	1.65 (1.18, 2.29)	0.003	1.23 (0.85, 1.79)	0.26
Asian (vs. White)	0.73 (0.09, 5.68)	0.76	0.73 (0.09, 5.98)	0.77
Other races (vs. White)	1.11 (0.70, 1.78)	0.65	0.90 (0.54, 1.50)	0.68
Smoking Status				
Current (vs. never)	2.15 (1.47, 3.16)	<0.001	2.49 (1.63, 3.81)	<0.001
Past (vs. never)	1.60 (1.03, 2.48)	0.04	1.93 (1.21, 3.09)	0.006
History of alcoholism/alcohol abuse	1.55 (1.07, 2.25)	0.02	1.32 (0.88, 1.99)	0.17
Total/HDL Cholesterol ratio	0.94 (0.87, 1.02)	0.11	—	—
Body mass index (per kg/m ²)	1.04 (1.02, 1.07)	0.001	1.03 (1.00, 1.06)	0.07
Diabetes mellitus (Y vs. N)	2.36 (1.44, 3.87)	<0.001	2.28 (1.33, 3.91)	0.003
Blood pressure-lowering drugs use	1.04 (0.72, 1.51)	0.83	—	—
Lipid lowering drugs use	0.82 (0.53, 1.25)	0.34	—	—
Years since HIV diagnosis	1.00 (0.97, 1.03)	0.96	—	—
Baseline CD4 (per 100 cells/mm ³)	1.01 (0.95, 1.07)	0.79	—	—
Baseline HIV-RNA and ART Status			—	—
On ART, HIV-RNA > 400 (vs. off ART)	0.66 (0.40, 1.09)	0.10	—	—
On ART, HIV-RNA ≤ 400 (vs. off ART)	1.08 (0.74, 1.58)	0.69	—	—
Interleukin-6 (per log ₂)	1.11 (0.96, 1.28)	0.16	—	—
C reactive protein (per log ₂)	1.10 (1.00, 1.20)	0.04	1.03 (0.94, 1.13)	0.56
Any ECG abnormalities (Y vs. N)	1.07 (0.79, 1.45)	0.65	—	—
Prior cardiovascular disease	1.24 (0.67, 2.31)	0.49	—	—

* Incident widened spatial QRS-T angle defined as developing a new angle ≥ 93 degrees in males and ≥ 74 degrees in females.

[†] Variables with significant association in the univariate model are entered in together in the multivariable model along with treatment arm and demographics

Table 3

Baseline factors associated with change in spatial QRST angle overtime using linear regression analysis

	Univariate Models		Multivariable Model*	
	Difference [95% CI]	P	Difference [95% CI]	P
Spatial QRST angle at baseline	−0.21 (−0.25, −0.17)	<0.001	−0.20 (−0.24, −0.16)	<0.001
Treatment Group (DC vs. VS)	2.62 (0.98, 4.27)	0.002	2.93 (1.34, 4.52)	<0.001
Age (year)	−0.04 (−0.13, 0.05)	0.38	0.02 (−0.07, 0.11)	0.66
Gender (Female vs. Male)	4.04 (2.19, 5.90)	<0.001	−0.94 (−3.02, 1.14)	0.37
Race				
Black (vs. White)	4.51 (2.71, 6.30)	<0.001	2.76 (0.88, 4.64)	0.004
Asian (vs. White)	3.96 (−4.87, 12.78)	0.38	2.84 (−5.73, 11.41)	0.52
Other Races (vs. White)	4.73 (2.31, 7.14)	<0.001	2.66 (0.26, 5.06)	0.03
Smoking Status			–	
Current (vs. Never)	0.47 (−1.46, 2.40)	0.63	–	–
Past (vs. Never)	0.89 (−1.30, 3.08)	0.42	–	–
History of alcoholism/alcohol abuse	1.60 (−0.63, 3.83)	0.16		
Total/HDL Cholesterol ratio	−0.39 (−0.71, −0.07)	0.02	−0.15 (−0.47, 0.17)	0.34
Body mass index (per kg/m ²)	0.22 (0.07, 0.38)	0.004	0.16 (0.01, 0.31)	0.04
Diabetes (Y vs. N)	2.09 (−1.23, 5.41)	0.22	–	–
Blood pressure-lowering drugs use	−0.33 (−2.38, 1.72)	0.75	–	–
Lipid lowering drugs use	−2.94 (−5.13, −0.74)	0.009	−2.30 (−4.52, −0.08)	0.04
Years since HIV diagnosis	−0.25 (−0.42, −0.08)	0.004	−0.13 (−0.30, 0.04)	0.14
Baseline CD4 (per 100 cells/mm ³)	−0.00 (−0.00, 0.00)	0.44	–	–
Baseline HIV-RNA and ART Status				
On ART, HIV-RNA > 400 (vs. off ART)	−0.09 (−2.65, 2.46)	0.94	–	–
On ART, HIV-RNA ≤ 400 (vs. off ART)	−0.43 (−2.55, 1.70)	0.69	–	–
Interleukin-6 (per log ₂)	0.39 (−0.41, 1.19)	0.33	–	–
hs-C reactive protein (per log ₂)	0.40 (−0.08, 0.88)	0.10	–	–
Any ECG abnormalities (Y vs. N)	0.92 (−0.73, 2.57)	0.27	–	–
Prior cardiovascular disease	−1.67 (−5.30, 1.96)	0.37	–	–

* Variables with significant association in the univariate model are entered in together in the multivariable model along with treatment arm and demographics