Electrocardiographic abnormalities among people with HIV in Shanghai, China

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SUMMARY People living with HIV (PLWH) have an excess risk of cardiovascular diseases (CVD). Electrocardiographic (ECG) abnormalities are independently predictive of incident cardiovascular events in the general population. Our study aimed to evaluate the prevalence and correlates of ECG abnormalities among PLWH in Shanghai, China. We used a cross-sectional design to collect data from Shanghai Public Health Clinical Center, China. A total of 587 HIV-infected patients aged between 18 and 75 years were recruited between January 2015 and February 2016. The overall prevalence of any type of ECG abnormalities was 53.3%. The prevalence of sinus tachycardia, ST-T segment elevation and left ventricular hypertrophy was 23.0%, 18.1%, and 6.8%, respectively. Multivariable logistic regression analysis indicated that ST-T segment elevation was positively associated with higher baseline HIV viral load ($\geq 4 \log_{10}$ copies/mL), and sinus tachycardia was negatively associated with older age but positively associated with lower CD4 cell count, higher baseline HIV viral load ($\geq 4 \log_{10}$ copies/mL) and higher lactate dehydrogenase (LDH) level ($\geq 133$ mg/dL). Any coded ECG abnormality was positively associated with higher baseline HIV viral load ($\geq 4 \log_{10}$ copies/mL). ECG abnormalities including sinus tachycardia and ST-T segment elevation are prevalent among Chinese HIV patients, which are significantly associated with immunodeficiency and HIV viral load. Routine ECG screening may be an important part of HIV clinical care in China.

Keywords HIV, ECG, antiretroviral therapy, sinus tachycardia, ST-T segment elevation

1. Introduction

Wide access to highly effective combination antiretroviral therapy (ART) has ostensibly changed HIV infection status in many parts of the world from a fatal diagnosis to a chronic condition. However, extended life expectancy comes with long-term noninfectious comorbidities (NICMs), such as cardiovascular disease (CVD) (1). Prior studies have demonstrated that CVD is more common among the HIV-infected population than HIV-uninfected controls (2,3). This increased risk was partly explained by traditional risk factors of CVD such as smoking, diabetes, age, gender, as well as HIV infection itself, such as CD4 cell count and/or viral load, which is known to cause inflammation response by oxidative stress or coagulation disorders (4-6). However, the relative contributions of conventional cardiovascular risk factors, metabolic side effects of ART, and HIV infection itself on CVD risk are difficult to identify, as these factors frequently occur simultaneously (7).

Due to its wide availability, low cost and the accumulating evidence that electrocardiographic (ECG) abnormalities are predictive of incident cardiovascular events in the general population (8), the 12-lead electrocardiogram is a very useful non-invasive tool for evaluation of cardiac disorders and risks in clinical settings. Several typical ECG parameters, including resting heart rate and markers of abnormal cardiac depolarization/repolarization, have been previously reported to be associated with increased risk of sudden cardiac death (SCD) (9,10). Cardiovascular involvement in HIV/AIDS was recognized as part of the pandemic and a wide spectrum of cardiovascular abnormalities including corrected QT (QTc) prolongation, widened spatial QRS-T angle, ST-segment depressions, T-wave changes, and resting heart rate have been widely reported (11-13). Moreover, the association between age, obesity, alcohol consumption, lower CD4 cell count and LV diastolic dysfunction and ECG abnormalities were documented among HIV-positive patients (14,15).
The limited literature suggests that CVD risks (e.g. carotid intima-media thickness [cIMT], chronic kidney disease [CKD], hypertension, glycometabolism abnormalities) are prevalent among HIV-infected patients in China (16-18), but data for ECG manifestations in this population are lacking. To fill this gap, we conducted a cross-sectional study to investigate the prevalence and correlates of ECG abnormalities among PLWH in Shanghai.

2. Materials and Methods

2.1. Study sample and data collection

All HIV-infected inpatients admitted to Shanghai Public Health Clinical Center routinely received a standardized comprehensive physical examination. For the present study, all HIV-infected inpatients aged between 18 and 75 years with ECG records during the study period from January 2015 to February 2016 were included in the final analysis. In brief, a structured anonymous questionnaire was developed to extract data from the hospital’s electronic medical records (EMR) system, including demographic data such as gender, age and marital status, and blood biochemical data such as fasting glucose, triglyceride (TG; mmol/L), total cholesterol (TC; mmol/L) and lactic dehydrogenase (LDH; u/L), as well as HIV-specific characteristics such as CD4 cell count, plasma HIV viral load, and ART regimens, etc. Hyperlipidemia was defined as TG ≥ 1.7mmol/L or TC ≥ 5.2 mmol/L, and high level of LDH was defined as LDH ≥ 245 u/L, according to recommendations by World Health Organization (WHO) and China national guidelines. The study was approved by the Institutional Review Board (IRB) of Fudan University, Shanghai, China.

2.2. ECG examination and categorization

Identical electrocardiographs [EDAN SE-1201 PC ECG system, EDAN Instruments, Inc.,China] were operating at 1000 samples per second with a frequency response of 0.05 Hz to 150 Hz., and standard 12-lead ECG was performed on all subjects in a supine position after 5 min rest using strictly standardized procedures. ECG examination was performed and initially read by an experienced cardiologist blinded to the patients’ clinical history, and reconfirmed by a senior cardiologist. In brief, a resting ECG with a SE-12 Express machine was employed, with the participant in the left lateral decubitus position. ECG abnormalities including arrhythmia, abnormalities of the QRS complex, hypotrophy of the ventricles, atrial dilation, and abnormal repolarization were recorded. ECG abnormalities were categorized into ten groups: sinus tachycardia, ST-T segment elevation, left ventricular hypertrophy, atriorentricular conduction abnormalities, axis deviation, sinus bradycardia, atrial fibrillation/flutter, ventricular tachycardia/fibrillation, ischaemic ECG findings and others.

2.3. Statistical analyses

Sociodemographic and HIV-related characteristics of study participants were tabulated with frequencies and proportions for categorical variables. Number and proportion of participants with ECG manifestations were also tabulated. Univariate and multivariate logistic regression analyses with calculations of odd ratio (OR) and 95% confidence intervals (CI) were performed to evaluate correlates of ST-T segment elevation, sinus tachycardia and any coded ECG abnormality. Variables with $p < 0.10$ in univariate analysis were subject to multivariate regression analysis for adjustment of potential confounders. Age was categorized into four groups: 18-29, 30-44, 45-59, 60-75 years. Pearson $\chi^2$ test and linear trend $\chi^2$ test were performed to assess the distribution and trend of ECG manifestations across the age groups. A 2-sided $P$ value < 0.05 was regarded as being statistically significant. All the statistical analyses were performed under SAS software Version 9.3. (IBM Company, New York, USA).

3. Results

3.1. Demographic and clinical characteristics

As shown in Table 1, the median age of the participants was 39.0 (IQR: 30.0-53.0) years. Among them, 90.1% were male, 41.2% were currently married, 27.3% were local registered residents, 29.3% were infected with HIV through homosexual behaviors whereas 55.7% through heterosexual behaviors.

As for the comorbidities, 36.1% were diagnosed with lung infection, 23.3% with tuberculosis, 5.3% with diabetes and 3.2% with kidney disease; 36.1% were tested with dyslipidemia (i.e., TG ≥ 1.7mmol/L or TC ≥ 5.2 mmol/L) and 45.8% were with LDH above cutoff level (i.e., >245 u/L) (Table 1).

3.2. HIV-specific Characteristics

Over two-thirds (68.5%) of the participants had plasma HIV viral load ≥ 4 log$_{10}$ copies/mL and 77.0% had CD4 cell count < 200 cells/μL. About 47.0% of the participants were on ART, of whom 72.5% had been on treatment for ≤ 2 years, 80.0% received a first-line regimen of "2 Nucleoside reverse transcriptase inhibitor (NRTI)+1 Non-nucleoside reverse transcriptase inhibitor (NNRTI) (e.g. Nevirapine [NVP]/Efavirenz [EFV])" and 18.5% received "2NRTI/NNRTI+Protease inhibitors (PI)" treatment. (Table 1).

3.2. Prevalence of abnormal ECG manifestations

The overall prevalence of any coded ECG abnormalities
was 53.3%. The most common abnormal ECG manifestation was sinus tachycardia (23.0%) and ST-T segment elevation (18.1%) (Table 2). Other prevalent ECG abnormal manifestations included left ventricular hypertrophy (6.8%), atrioventricular conduction abnormalities (5.1%) and sinus bradycardia (4.8%) (Table 2). Figure 1 further presents the age-specific prevalence of abnormal ECG manifestations. Both the prevalence of ST-T segment elevation (Pfor linear trend < 0.001) and the prevalence of left ventricular hypertrophy (Pfor linear trend < 0.001) increased as age increased, whereas the prevalence of sinus tachycardia decreased as age increased (Pfor linear trend < 0.001) (Figure 1).

3.3. Correlates of ST-T segment elevation, sinus tachycardia and any coded ECG abnormalities

### Table 1. Characteristics of HIV-positive study participants (N = 587)

| Characteristics                                       | No. (proportion, %) |
|--------------------------------------------------------|---------------------|
| Age, years                                             |                     |
| Median (IQR)                                           | 39.0 (30.0-53.0)    |
| 18-29                                                  | 141 (24.0)          |
| 30-44                                                  | 223 (38.0)          |
| 45-59                                                  | 140 (23.8)          |
| 60-75                                                  | 83 (14.2)           |
| Male sex                                               | 529 (90.1)          |
| Current married                                        | 242 (41.2)          |
| Local residents                                        | 160 (27.3)          |
| Route of HIV transmission                              |                     |
| Homosexual                                             | 172 (29.3)          |
| Heterosexual                                           | 327 (55.7)          |
| others                                                 | 88 (15.0)           |
| Comorbid condition                                     |                     |
| Lung infection                                          | 212 (36.1)          |
| Tuberculosis                                            | 131 (22.3)          |
| Diabetes                                               | 31 (5.3)            |
| Kidney disease                                         | 19 (3.2)            |
| Plasma biochemical tests                               |                     |
| Dyslipidemia                                           | 212 (36.1)          |
| LDH ≥ 245, U/L                                         | 269 (45.8)          |
| HIV-specific characteristics                           |                     |
| Years since HIV diagnosis ≥ 3                          | 96 (16.4)           |
| CD4 cells < 200, cells/mL                              | 452 (77.0)          |
| Baseline Viral load ≥ 4, (log_{10} copies/mL)          | 402 (68.5)          |
| On cART                                                | 276 (47.0)          |
| 2NRTI+NNRTI (NVP/EFV)                                  | 221 (38.0)          |
| 2NRTI/NNRTI+PI                                        | 51 (18.5)           |
| Other cART regimen*                                    | 4 (1.5)             |
| Duration of cART ≤ 2 years                             | 200 (72.5)          |
| Duration of cART > 2 years                             | 76 (27.5)           |

*Including PI only or 2NRTI+RAL. Dyslipidemia defined as TG ≥ 1.7mmol/L or TC ≥ 5.2 mmol/L. IQR, Interquartile range; LDH, Lactic dehydrogenase; cART, Combination antiretroviral therapy; NRTI: Nucleoside reverse transcriptase inhibitor; NNRTI: Non-nucleoside reverse transcriptase inhibitor; NVP: Nevirapine; EFV: Efavirenz; PI: Protease inhibitors; RAL: Raltegravir.

### Table 2. Prevalence of ECG abnormalities among the study participants

| ECG abnormalities                                      | No. (proportion, %) |
|--------------------------------------------------------|---------------------|
| Any coded ECG abnormalities                            | 312 (53.3)          |
| Sinus tachycardia                                      | 136 (23.0)          |
| ST-T segment elevation                                 | 106 (18.1)          |
| Left ventricular hypertrophy                           | 40 (6.8)            |
| Atrioventricular conduction abnormalities               | 30 (5.1)            |
| Axis deviation                                         | 30 (5.1)            |
| Sinus bradycardia                                      | 28 (4.8)            |
| Atrial fibrillation/flutter                             | 18 (3.1)            |
| Ventricular tachycardia/fibration                      | 14 (2.4)            |
| Ischaemic ECG findings                                 | 3 (0.5)             |
| Others*                                                | 24 (4.1)            |

*Including low voltage of limb leads, junctional rhythm, right ventricular hypertrophy, sinus bigeminy, clockwise transposition and pacing rhythm.

**Figure 1. Prevalence of electrocardiography (ECG) abnormalities among HIV-positive participants by age group (*** P for linear trend < 0.001).**
Table 3 presents results of three separate multivariable logistic regression analyses with adjustment of potential confounders to explore correlates of ST-T segment elevation, sinus tachycardia and any coded ECG abnormality among HIV-positive participants, respectively.

4. Discussion

ECG examination is a useful screening tool for CVDs, particularly in resource limited settings. This is particularly relevant for HIV patients who are expected to live much longer but with high probability of living with CVDs in the era of combination ART (19). Previous studies revealed that prolonged Q-T interval, a precursor to fatal cardiac arrhythmias, is the most prominent ECG manifestation among HIV patients (20). However, such data are not available for Chinese HIV patients who may also experience high prevalence of subclinical atherosclerosis (21). In the present study, we observed relatively high prevalence of sinus tachycardia and ST-T segment elevation in HIV-positive individuals, although the prevalence is slightly lower than that reported by studies in south-east Africa (22,23). Such differences reflect global diversities in a confluence of CVD risk factors that may or may not be directly associated with HIV among PLWH, such as environmental exposures, lifestyle, nutrition, coinfections, access to ART and healthcare continuum (24-26).

Notably, the prevalence of ECG abnormalities among HIV patients in this study is greater than that of the Chinese general population aged above 65 years (27). This suggests early onset of adverse cardiovascular affects by HIV infection, which are most likely associated with immune activation and inflammatory response but independent of classic CVD risk factors and could occur at younger ages (27). The increasing risks of sinus bradycardia, ST-T segment elevation and left ventricular hypertrophy among older patients underscore the importance of enhanced ECG monitoring and cardiovascular alerts for HIV-infected elders.

The prevalence of sinus tachycardia was higher than any other ECG abnormality among HIV patients in this study. This pattern has also been observed in other...
studies (11,28). High heart rate has been observed as an independent risk factor for cardiovascular morbidity and mortality in the general population. In addition to negative association between older age and sinus tachycardia, which is well represented in the general population, lower CD4 cell count or more severe immunodeficiency and higher lactic dehydrogenase (LDH) level were positively associated with sinus tachycardia. Previous studies suggest that HIV infection with low CD4 cell count might further contribute to cardiovascular complications (29). The relationship between the CD4 cell count and cardiac complications may be mediated through the role of heightened inflammation and serum levels of inflammatory mediators, which likely occurred in patients with low CD4 cell count thereby predisposing them to sinus tachycardia (30,31). In advanced HIV disease, depletion of the CD4 cell count leads to the activation of CD8 killer T-cells which mediate persistent immune dysfunction and inflammation (32,33). On the other hand, LDH is associated with sinus tachycardia because it is a marker of common injuries and diseases such as myocardial infarction (MI) and heart failure and is released during tissue damage.

ST-T segment elevation on ECG is observed in HIV-infected patients in this study, which could be caused either by pericardial disease or dilated cardiomyopathy, that are known to occur frequently in HIV-positive individuals (34-36). Meanwhile, those who had higher levels of plasma HIV viral load had a greater risk of ST-T segment elevation and any coded ECG finding as well. Such associations were also observed in the VACS study (37). The HIV virus causes inflammatory reaction in the coronary vessels and myocardial cells, which is believed to promote endothelial dysfunction and atherosclerosis as well as early carotid artery atherosclerosis (38,39). In fact, HIV genomic sequences have been demonstrated in the coronary vessels of HIV-infected patients who died of acute myocardial infarction (40), reiterating that HIV infection is an independent risk for ECG abnormality by itself regardless of other traditional CVD risk factors. Nonetheless, the exact mechanism(s) need further investigation.

We did not observe any association of ART status or usage of antiretroviral drugs (ARV) with ECG abnormalities in this study, probably due to the low proportion of being treated and the short duration of ART for those treated. Untreated HIV patients had severe immunodeficiency and high HIV viral load, which were associated with high risk for CVD and ECG abnormalities. On the other hand, there is growing evidence that dyslipidemia and endothelial dysfunction are common side effects of ART particularly among patients receiving PIs (41,42). Longer duration of ART would also expose the patients to higher risk for CVD and higher likelihood of abnormal ECG manifestations. As the national ART program rapidly scales up and the availability of PIs increases in China, cardiovascular side effects and related ECG abnormalities are not ignorable and very likely to increase substantially.

This study had several limitations. First, only prevalence rather than incidence of ECG abnormalities could be investigated due to the cross-sectional nature of this study. Future longitudinal studies are needed to examine the incidence and causal mechanisms of CVDs and characteristic ECG manifestations. Second, this study was conducted in a municipal clinical center, which is the officially designated hospital for HIV care and treatment in Shanghai, China. Therefore, the study results may not be generalizable to other provinces. Multicenter studies are warranted in the near future. Third, no HIV-negative controls were enrolled for comparison in this study, further limiting our ability to draw a promising conclusion.

In summary, this exploratory study reveals high prevalence of typical ECG abnormalities including sinus tachycardia and ST-T segment elevation among the HIV-positive population in China, which could be employed as a useful screening tool for CVDs in Chinese HIV patients who are mostly living in rural areas and have limited access to comprehensive clinical care. The associations of ECG abnormalities with immunodeficiency and HIV viral load highlight the necessity of early and combined ART for prevention of cardiovascular comorbidities, which could also be adverse consequences of cART. This dilemma further underscores needs of careful monitoring and care continuum for CVDs in the era of combination ART scale up in China.

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