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Original Article

Estimated risk of cardiovascular disease among the HIV-positive patients aged 40 years or older in Taiwan

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Atherosclerotic cardiovascular disease (ASCVD);
Data-collection on adverse effects of anti-HIV drugs (D:A:D);
Antiretroviral therapy

Abstract *Background:* Cardiovascular disease (CVD) is an emerging cause of morbidity and mortality among HIV-positive patients receiving successful combination antiretroviral therapy, but their CVD risk has been rarely investigated in Asia—Pacific region. We aimed to assess the CVD risk of HIV-positive Taiwanese outpatients.
Methods: We did cross-sectional questionnaire interviews to collect information of HIV-positive Taiwanese patients aged 40—79 at the HIV clinics of a medical center from 1 March to 31 August, 2017. The Framingham Risk Score (FRS), Atherosclerotic Cardiovascular Disease (ASCVD) risk score and Data-Collection on Adverse effects of Anti-HIV Drugs (D:A:D) risk score were used to estimate their CVD risk.
Results: Of the screened 1251 patients, 1006 (80.4%) with complete data to assess their CVD risk were included for analyses. The prevalence of patients aged 40—75 and with a high CVD risk was 30.6% by FRS, 3.7% by D:A:D (R) risk score, and 22.2% by ASCVD risk score. In multiple logistic regression, older age, current smoking, higher systolic blood pressure, and higher triglyceride and fasting glucose levels were independently associated with the ASCVD risk score $\geq$7.5%. If current smokers aged 55—59 had stopped smoking, the proportions of them with a 10-year CVD risk of $\geq$10% by FRS and $\geq$7.5% by ASCVD risk score would have decreased by 35.3% and 20.0%, respectively.

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Conclusions: Higher CVD risk estimates among HIV-positive Taiwanese aged 40—75 were associated with an older age, current smoking, higher systolic blood pressure, hypertriglyceridemia, and hyperglycemia. Smoking cessation could potentially lead to significant decreases of CVD risk.

Introduction

Combination antiretroviral therapy (cART) has dramatically improved the survival of people living with HIV infection.[1,2] As a result, the increased life expectancy has led to an epidemiological shift of the comorbidities from acquired immunodeficiency syndrome (AIDS)-related opportunistic illnesses to non-AIDS-related diseases, such as dyslipidemia, hypertension, diabetes mellitus (DM), chronic kidney disease, reduced bone mineral density, cardiovascular disease (CVD), and non-AIDS-related malignancies.[3,4] Similar to other non-AIDS-related diseases, CVD events in HIV-positive patients have been reported to occur at higher rates compared with those in HIV-negative or general population.[4—8] Although the traditional CVD risk factors, such as smoking, are commonly present in the HIV-positive population, a complex interplay between CVD and HIV-related chronic inflammation and side effects of cART, such as protease inhibitors and abacavir-implicated cardiovascular toxicity,[7—12] and tenofovir disoproxil fumarate-related nephrotoxicity.[13]

Smoking is one of the largest contributors to myocardial infarction (MI) worldwide and possibly one of the predominantly modifiable risk factors for MI among HIV-positive patients.[7,14,15] A Danish HIV Cohort Study showed that smoking cessation could potentially prevent more than 40% of MI among HIV-positive patients.[15] Another follow-up study by Data-Collection on Adverse effects of Anti-HIV Drugs (D:A:D) Study Group also showed that the risk of CVD events decreased with the increasing duration of smoking discontinuation.[16] Therefore, the European AIDS Clinical Society (EACS) guidelines suggest smoking cessation to reduce the risk of tobacco-related diseases, slow the progression of existing tobacco-related disease, and improve life expectancy.[17] Moreover, the EACS guidelines also suggest that all HIV-positive men aged over 40 years and HIV-positive women over 50 years who have no CVD should have the assessment of CVD risk by Framingham Risk Score (FRS)[18] every two years.[17] However, previous studies inconsistently reported that FRS might underestimate or overestimate CVD risk in HIV-positive population.[19,20] In addition to FRS, there are other validated tools to assess the CVD risk that are commonly used in HIV-positive population,[19—25] such as the Atherosclerotic Cardiovascular Disease (ASCVD) risk score recently published in the American College of Cardiology/American Heart Association guidelines[26] and the D:A:D risk scores.[27]

The estimated CVD risk can be used to quantify risk and to guide preventive care.[18,27] However, the risk of CVD has rarely been investigated in the HIV-positive patients in Asia. In this study, we aimed to assess the 10-year CVD risk with the use of the FRS, ASCVD risk score, and 5-year CVD risk by D:A:D (R) risk score among HIV-positive patients in an outpatient setting at a medical center, to identify the most significant associated factors with high CVD risk by the three prediction models, and to quantify the impact of smoking cessation on CVD risk if the patients who were current smokers had stopped smoking hypothetically.

Methods

Study design and setting

This was a cross-sectional study that recruited all HIV-positive outpatients seeking medical attention in the HIV outpatient clinics at the National Taiwan University Hospital between March and August, 2017. A standardized case record form was used to collect information on demographics, body-mass index (BMI), self-reported smoking status (current, former, or never smoking), blood pressure, use of hypoglycemic, lipid-lowering, or antihypertensive agents, serum lipid levels (total cholesterol, high-density lipoprotein cholesterol [HDL-C]), and triglycerides, self-reported comorbidities (such as coronary artery disease [CAD], hypertension, and DM), and family history of CAD, hypertension, and DM. HIV-related clinical data included regimens of cART, CD4 cell counts and plasma HIV RNA loads. The study was approved by the Research Ethics Committee of the National Taiwan University Hospital (registration number: 201003112R) and written informed consents were obtained from all of the participants.

According to the national HIV treatment guidelines in Taiwan, HIV-positive patients are provided with free-of-charge access to HIV care, including cART and monitoring of CD4 count and plasma HIV RNA load. While CD4-guided initiation of cART had been recommended in the past, antiretroviral-naïve patients have been counseled to start cART regardless of CD4 count since 2015. Once cART is initiated, follow-up of treatment responses would be assessed every 3 months in the first year of cART and, thereafter, every 6 months once the patients have achieved viral suppression and been in a stable condition.[28]

Clinical measurements

The systolic and diastolic blood pressures were assessed after the subjects had seated and rested for at least 5 min. The height was determined without shoes by the same

machine and the weight was measured by a digital scale, and patients were fully dressed without shoes or heavy clothing. The BMI was calculated as the weight in kilograms divided by the square of the height in meters.

CVD risk assessment

We used three CVD risk prediction models, including the FRS, D:A:D reduced (D:A:D [R]) and ASCVD risk score. The 10-year CVD risk was assessed in all patients aged 30—75 years by the FRS, a model that comprises age, gender, total cholesterol and HDL-C levels, systolic blood pressure, use of antihypertensive medication, and smoking status.[18] For comparison among the three risk models and other studies,[20,21] we categorized the participants as being at low (<10%) and high (≥10%) CVD risk by the FRS. The D:A:D (R) model risk equation uses age, gender, family history of CVD, smoking, DM, total cholesterol, HDL-C, and systolic blood pressure to predict the 5-year CVD risk.[27] It has been suggested that the threshold of the high 5-year global CVD risk estimates by the D:A:D (R) model would be around 10%. This model is only valid for HIV-positive patients aged 18—75 years and ART covariates are omitted, however.[27] The American Heart Association ASCVD model includes age, gender, total cholesterol and HDL-C levels, systolic blood pressure, use of antihypertensive medication, smoking status, and DM.[26] This score estimates a 10-year risk for ASCVD for patients aged 40—79 years, and a score of ≥7.5% was considered high risk for CVD.[26] Because each prediction model applied to different age groups, this study included only patients aged 40—75 years for analyses.

Laboratory investigations

Total cholesterol, triglyceride, glucose, HDL-C, and low-density lipoprotein cholesterol (LDL-C) levels were determined after at least an 8-h fasting. Plasma HIV RNA load was quantified using the Cobas Amplicor HIV-1 Monitor test (Cobas Amplicor version 1.5, Roche Diagnostics Corporation, IN, USA) with the lowest detection limit of 20 copies/mL. CD4 counts were determined using FAC Flow (BD FACS Calibur, Becton Dickinson, CA, USA), hepatitis B surface antigen (HBsAg) and anti-HBs antibody (anti-HBs) using quantitative determination, hepatitis B core antibody (anti-HBc) and antibodies to hepatitis C virus (anti-HCV) using qualitative detection and chemiluminescent microparticle immunoassay (Abbott Architect i2000SR, Abbott Diagnostics, Abbott Park, IL, USA).

Statistical analysis

SAS (version 9.3) was used for all analyses. Categorical variables were compared using χ^2 or Fisher's exact test, whereas non-categorical variables were compared using the Student *t* test. To quantify the risk reduction by smoking cessation, we recalculated the risk scores of the current smokers by changing their status of smoking to non-smoking followed by calculating the risk changes. Significant variables associated with high CVD risk in univariate analysis were entered into a multiple logistic regression. Only variables with a two-sided *p* value of less than 0.05 were considered statistically significant.

Results

In the 5-month study period, 2808 patients were screened and 1251 (44.6%) were aged ≥40 years, of whom 1006 (80.4%) patients aged 40—75 years had complete data for the assessment of their CVD risk after the exclusion of 214 patients with incomplete data, 11 aged >75 years, and 20 with a prior history of CAD (Fig. 1). The clinical characteristics of the included 1006 patients are shown in Table 1. The participants were predominately male (93.2%), with a mean age of 49.3 years, CD4 count of 620 cells/mm^3, and plasma HIV RNA load of 1.42 $\log_{10}$ copies/ml, and 98.5% had been receiving cART before the survey was conducted.

The prevalence of patients aged 40—75 years with a high CVD risk was 30.6% by FRS, 3.7% by D:A:D (R), and 22.2% by ASCVD. The percentages of patients with high CVD risk determined by the three prediction models by age groups are shown in Fig. 2. The older age group the patients belonged to, the higher the percentages of the patients with high CVD risk by all of the three prediction models were.

Comparisons of demographic and clinical characteristics of HIV-positive patients with a high and low CVD risk determined by the three different risk models are shown in Table 2. Factors associated with a high CVD risk estimated by the three prediction models by logistic regression are shown in Table 3. Older age, current smoking, higher blood pressure, and higher triglyceride and fasting glucose levels were significantly associated with a high CVD risk in all of the three prediction models.

To quantify the potential impact on the risk reduction by smoking cessation among the current smokers, we re-calculated the CVD risk by changing their status of smoking to non-smoking. In this hypothetical intervention by stopping smoking, the proportions of the current smokers aged 55—59 years with a 10-year CVD risk of ≥10% by FRS and ≥7.5% by ASCVD would have decreased by 35.3% and 20.0%, respectively (Fig. 3).

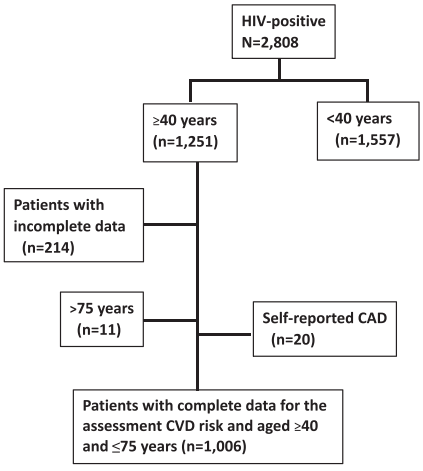

Figure 1. Study flow.

Table 1 Baseline characteristics of the included 1006 patients aged 40—75 years and with complete data.

Characteristic	N = 1006
Male, n (%)	938 (93.2)
Age, mean (SD), years	49.3 (7.6)
Plasma HIV RNA load, mean (SD), log_{10} copies/ml	1.42 (0.5)
CD4, mean (SD), cells/mm^3	620 (285)
On cART, n (%)	991 (98.5)
Positive anti-HCV, n (%) (n = 820[a])	105 (12.8)
Positive HBsAg, n (%) (n = 751[a])	146 (19.4)
Positivity anti-HAV, n (%) (n = 930[a])	794 (85.4)
Body-mass index, mean (SD), kg/m^2	24.0 (3.6)
Systolic blood pressure, mean (SD), mmHg	128 (17.7)
Diastolic blood pressure, mean (SD), mmHg	80 (12.0)
TG, mean (SD), mg/dl	161 (134)
Total cholesterol, mean (SD), mg/dl	173 (35)
HDL cholesterol, mean (SD), mg/dl	44 (12)
Smoking status, n (%)	
Never	470 (46.7)
Past	217 (21.6)
Current	319 (31.7)
Self-reported comorbidities, n (%)	
Diabetes mellitus	75 (7.5)
Hypertension	114 (11.3)
Concurrent medications, n (%)	
Lipid-lowering agents	96 (9.5)
Hypoglycemics	75 (7.5)
Anti-hypertensives	140 (13.9)
Self-reported family history, n (%)	
Diabetes mellitus	325 (32.3)
Hypertension	572 (56.9)
Family history of CAD	162 (16.1)

Abbreviations: cART, combination of antiretroviral therapy; CAD, cardiovascular disease; HDL, high-density lipoprotein; SD, standard deviation; TG, triglyceride.
[a] The number of patients with data.

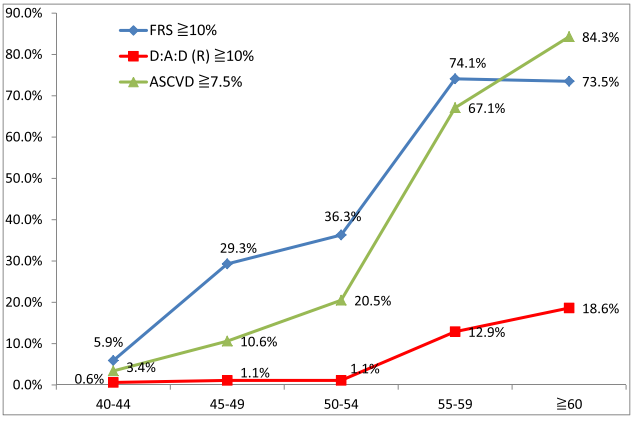

Figure 2. The percentages of patients with high-risk cardiovascular disease (CVD) risk estimates determined by the three prediction models by age groups.

Discussion

In this study, we found the prevalence of patients aged 40—75 years who were estimated to have a high CVD risk was 30.6% by FRS (CVD risk ≥10%), 3.7% by D:A:D (R) (≥10%), and 22.2% by ASCVD (≥7.5%). The prevalence of CVD risk ≥10% among our participants is higher than that in other studies (30.6% vs. 4.5—13.5% by FRS, 3.7% vs. 0—4.4% by D:A:D (R)).[21—23,29] These discrepancies might result from the fact that our study population was older (mean age 49.5 vs. 36 years)[21,23] and had a higher proportion of patients receiving cART (98.5% vs. 0—66.3%) compared with those of other studies.[21—23] In contrast, the findings of our study are in line with those of the study by Krikke M et al.,[20] which shared similar characteristics of the participants with ours, such as mean age (49.3 vs. 46 years) and BMI (24 vs. 23.6 kg/m^2), and the proportions of current smokers (32% vs. 38%).[20]

Underestimation or overestimation of CVD risk in the HIV-positive population by FRS have been inconsistently reported since it does not take the risk associated with chronic inflammation or cART use into consideration,[19,20,24] while the D:A:D and ASCVD yield an overall comparable CVD risk.[20] Nevertheless, a large cohort study showed ASCVD and D:A:D underestimated the CVD risk, but FRS most accurately predicted events.[25] The discrepancies among these studies might be attributed to different end-point definitions used (including cardiac failure, transient ischemic attack in FRS; only including acute MI, stroke, coronary heart disease/stroke death in ASCVD; and including angina, unstable angina in D:A:D),[20] different follow-up durations (12 years in FRS, >12 years in ASCVD, and 4.8 years in D:A:D), age groups (30—75 years in FRS, 40—79 years in ASCVD, and 18—75 years in D:A:D), and study settings (general population in FRS, general population in ASCVD, and HIV-positive patients in Europe/Australia/USA in D:A:D) in the three CVD risk prediction models.[20] Thus, there are currently no agreed-on routine risk screening tools available to accurately detect early and subclinical diseases, although some experts favor ASCVD and D:A:D.[30]

The percentages of high CVD risk defined by the three prediction models increased in the older age groups in our study (Fig. 2). Factors significantly associated with high CVD risk by the three different risk prediction models in our analysis included older age, current smoker, higher systolic blood pressure, and higher triglyceride and fasting glucose levels (Table 3). Likewise, the study by Guo et al. also reported that older age and smoking were significantly associated with FRS ≥10% and ASCVD ≥10% among Chinese subjects.[21] As most of these risk factors are clearly modifiable except for age, clinicians should make every effort to correct these factors. For clinicians caring for HIV-positive patients, our findings provide additional evidence to support the importance of aggressive management of modifiable HIV-specific and traditional CVD risk factors, including avoidance of antiretroviral agents that have been noted to increase the risk of metabolic complications and CVD[4,22,23,31] and screening for and treatment of hypertension, dyslipidemia, and DM to reduce the overall burden of CVD in HIV-positive patients.

Table 2 Comparisons of characteristics of HIV-infected patients aged 40–75 years at high-risk and those at low risk for CVD by the three prediction models.

Variable	FRS		P =	D:A:D risk score		P =	ASVCD risk score		P =
	≥10% n = 308	<10% n = 698		≥10% n = 37	<10%, n = 969		≥7.5% n = 223	<7.5% n = 783	
Age, mean (SD), years	54.8 (8.1)	47.0 (5.9)	<0.0001	61.3 (8.4)	48.9 (7.1)	<0.0001	58.3 (8.3)	46.8 (5.0)	<0.0001
Gender, n (%)			<0.0001			0.317			0.745
Male	308 (100)	630 (90.3)		36 (97.3)	902 (93.1)		209 (93.7)	729 (93.1)	
Female	0	68 (9.7)		1 (2.7)	67 (6.9)		14 (6.3)	54 (6.9)	
Risk group, n (%)			0.136			0.134			0.001
MSM/Bisexual	281 (91.2)	609 (87.3)		31 (83.9)	859 (88.7)		186 (83.4)	704 (89.9)	
Heterosexual	18 (5.8)	67 (9.60)		6 (16.2)	79 (8.2)		32 (14.4)	53 (6.8)	
Other/IDU	9 (2.9)	22 (3.2)		0	31 (3.2)		5 (2.2)	26 (3.3)	
CD4 counts, mean (SD), cells/mm^3	617 (298)	622 (279)	0.847	624 (349)	620 (282)	0.944	628 (312)	618 (277)	0.681
Plasma HIV viral load, mean (SD), log_{10} copies/ml	1.37 (0.4)	1.44 (0.5)	0.015	1.47 (0.56)	1.41 (0.49)	0.529	1.40 (0.50)	1.43 (0.49)	0.523
Positive anti-HCV, n (%)	30 (12.4)	75 (13.0)	0.798	3 (10.3)	102 (12.9)	0.687	23 (13.5)	82 (12.6)	0.751
Positive HBsAg, n (%)	38 (16.7)	108 (20.6)	0.218	1 (3.6)	145 (20.1)	0.031	31 (19.4)	115 (19.5)	0.981
Smoking status, n (%)			<0.0001			<0.0001			<0.0001
Never	61 (19.8)	409 (58.6)		5 (13.5)	465 (48.0)		76 (34.1)	394 (50.3)	
Past	104 (33.8)	113 (16.2)		5 (13.5)	212 (21.9)		39 (17.5)	178 (22.7)	
Current	143 (46.4)	176 (25.2)		27 (72.9)	292 (30.1)		108 (48.4)	211 (26.9)	
BMI, mean (SD), kg/m^2	24.17 (3.6)	23.85 (3.5)	0.179	24.3 (4.0)	23.9 (3.5)	0.560	24.1 (3.6)	23.9 (3.5)	0.362
Obesity, BMI ≥27, n (%)	61 (19.9)	122 (17.5)	0.365	11 (29.7)	172 (17.8)	0.064	50 (22.4)	133 (17.0)	0.065
On cART, n (%)	305 (99.0)	686 (98.3)	0.369	36 (97.3)	955 (98.6)	0.536	221 (99.1)	770 (98.3)	0.407
Exercise, n (%)	100 (32.5)	286 (41.0)	0.011	7 (18.9)	379 (39.1)	0.013	62 (27.8)	324 (41.4)	0.0002
Systolic blood pressure, mean (SD), mmHg	132 (19.8)	125 (16.3)	<0.0001	133 (16.8)	127 (17.7)	0.077	136 (18.9)	125 (16.7)	<0.0001
Diastolic blood pressure, mean (SD), mmHg	81 (13.0)	78 (11.5)	0.0052	80 (12.3)	79 (11.9)	0.849	82 (12.3)	79 (11.7)	0.0001
TG, mean (SD), mg/dl	196 (184)	145 (101)	<0.0001	245 (314)	157 (122)	0.098	208 (202)	147 (104)	<0.0001
Total cholesterol, mean (SD), mg/dl	185 (35)	168 (34)	<0.0001	182 (31)	173 (35)	0.137	179 (34)	172 (36)	0.005
HDL cholesterol, mean (SD), mg/dl	42 (11.1)	45 (11.5)	0.001	38 (10.8)	45 (11.5)	0.001	40 (10.4)	46 (11.5)	<0.0001
Fasting glucose, mean (SD), mg/dl	103 (23.9)	96 (17.4)	<0.0001	122 (32.7)	97 (18.5)	0.0002	109 (28.3)	95 (15.5)	<0.0001

Abbreviations: ASCVD, the atherosclerotic cardiovascular disease risk score; BMI, body-mass index; cART, combination antiretroviral therapy; D:A:D, Data-Collection on Adverse effects of Anti-HIV Drugs; FRS, Framingham Risk Score; HDL, high-density lipoprotein; IDU, injecting drug user; MSM, men who have sex with men; SD, standard deviation; TG, triglyceride.

Table 3 Logistic regression analysis of factors associated a high CVD risk determined by the three prediction models.

Variable	FRS ≥10%		D:A:D risk score ≥10%		ASVCD risk score ≥7.5%	
	AOR	95% CI	AOR	95% CI	AOR	95% CI
Age (per 1-year increase)	1.242	1.201—1.286	1.328	1.222—1.444	1.565	1.446—1.694
Current smoking	5.739	3.741—8.803	105.55	22.057—505.066	38.27	16.360—89.522
BMI	1.025	0.970—1.082	0.984	0.874—1.108	1.002	0.922—1.090
Exercise	1.015	0.679—1.517	0.606	0.200—1.832	0.937	0.487—1.804
Systolic blood pressure (per 1-mm Hg increase)	1.016	1.000—1.033	1.045	1.000—1.093	1.071	1.044—1.100
Diastolic blood pressure (per 1-mm Hg increase)	1.007	0.984—1.031	0.995	0.928—1.067	1.012	0.976—1.049
Triglyceride (per 1-mg/dl increase)	1.004	1.002—1.006	1.002	1.000—1.004	1.005	1.003—1.007
HDL cholesterol (per 1-mm Hg increase)	1.000	0.983—1.018	0.951	0.907—0.998	0.929	0.899—0.961
Fasting glucose (per 1-mm Hg increase)	1.005	0.996—1.014	1.039	1.023—1.055	1.026	1.013—1.040

Abbreviations: 95% CI, 95% confidence interval; AOR, adjusted odds ratio; BMI, body-mass index; HDL, high-density lipoprotein.

Lower CD4 counts have also been shown to be associated with an increased risk of CVD in HIV-positive patients.[4,6,9,12] The HIV Outpatient Study (HOPS) prospective observation cohort study showed that CD4 count of 350 cells/mm^3 or less was significantly associated with CVD events (hazard ratio, 1.58 [95% confidence interval, 1.09—2.30]).[12] However, our study did not show the association between CVD risk and CD4 counts (Table 2). Such a discrepancy might be attributed to different study designs (cross-sectional vs. cohort), a higher mean CD4 count (620 vs. 395 cells/mm^3) and higher percentage of patients receiving cART in our study (98.5% vs. 75.1%),[12] and different end-points used (high CVD risks vs. CVD events). Given the fact that patients with lower on-therapy CD4 counts had higher non-AIDS and all causes mortality and age-related events,[32] efforts to early diagnose HIV infection and initiate cART cannot be overemphasized.

Current smoking is the most commonly reported CVD risk factors.[7,11,14,15] Benefits from smoking cessation to lower CVD risk have also been reported.[7,11,14—16,18] The present study quantified the risk reduction by hypothetical intervention of smoking cessation in HIV-positive population. This could support the advocate of smoking cessation as a priority in the long-term HIV care and persuade the patients to do so. According to the D:A:D study, the incidence rate ratio of CVD in patients stopping smoking during follow-up decreased from 2.32 in the first year of smoking cessation to 1.49 after >3 years of smoking cessation.[16] Successfully smoking cessation can reduce the overall CVD burden among HIV-positive patients and improve their life quality.

There are several limitations in our study. First, given the cross-sectional nature of the study design, we were not able to assess the accuracy of the prediction for the incident CVD events by the FRS, D:A:D (R) and ASCVD and provide the real-world risk reduction by smoking cessation. Second, data of biomarkers were not available in the clinical setting and we were not able to identify the association between inflammatory biomarkers and the CVD risk scores in the three prediction models. Third, as the majority of our subjects were men, reflecting the epidemiology of HIV infection in Taiwan, our results may not be generalizable to HIV-positive women.

We conclude that older age, current smokers, higher systolic blood pressures, triglyceride, and glucose levels were independently associated with high CVD risks by the three different risk prediction models in our study population. In the hypothetical intervention of smoking cessation, the proportions of the current smokers aged 55—59 years with a 10-year CVD risk of ≥10% by FRS and ≥7.5% by ASCVD would have decreased by 35.3% and 20.0%, respectively.

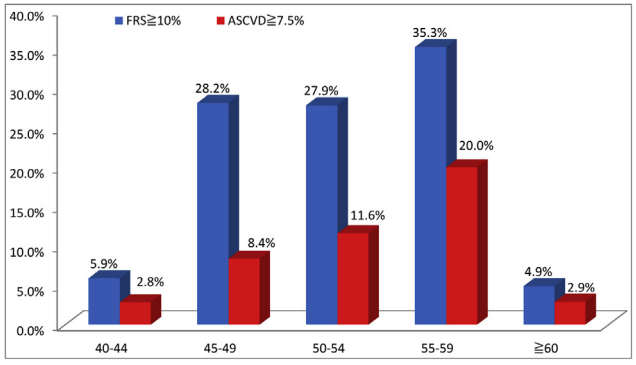

Figure 3. The decreases of percentages of the two prediction models (Framingham risk score and Atherosclerotic Cardiovascular Disease risk score) by age groups with hypothetical intervention of smoking cessation.

Conflicts of interest

C.-C. H. has received research support from Gilead Sciences, Merck, and ViiV and speaker honoraria from ViiV and Gilead Sciences, and served on advisory boards for Gilead Sciences and Janssen.

Other authors, none to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jmii.2019.03.006.