Jurnal Ners

Volume 21 Issue 1, February 2026, p. 67-75
http://dx.doi.org/10.20473/jn.v21i1.72933

Original Article

Open Access

Change in cardiovascular risk profile in people with human immunodeficiency virus infection: a-12 months follow up

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Responsible Editor: Rifky Octavia Pradipta

Received: 16 May 2025○ Revised: 8 February 2026 ○ Accepted: 22 February 2026

ABSTRACT

Introduction: Predicting cardiovascular disease (CVD) risk is crucial for primary prevention, particularly among adults living with HIV (PLHIV) who face elevated risks due to antiretroviral therapy and comorbidities. However, there is limited evidence on how CVD risk changes longitudinally and on the factors influencing these changes in this population. This study aimed to evaluate longitudinal changes in CVD risk and identify the contributing factors among HIV-positive individuals**.**

Methods: A 12-month prospective study was conducted at an AIDS treatment center in southern Taiwan. A total of 411 adults living with HIV, aged 18 years or older, with no history of CVD treatment, were enrolled. CVD risk was assessed at baseline and 6 and 12 months using the D:A:D risk prediction model. Mixed-effects models were used to examine associated factors.

Results: participants ranged in age from 19 to 77 years, with 95.9% being male. At baseline, 47% of the patients were low-risk, 37.7% were moderate-risk, 10.9% were high-risk, and 4.4% were very high-risk. After 12 months, 19% of participants showed a reduction in CVD risk. Increased risk was significantly associated with hepatitis C co-infection, use of lopinavir- or abacavir-based ART, and a longer duration of lopinavir exposure. Conversely, reductions in CVD risk were linked to higher educational attainment, use of antihypertensive or lipid-lowering therapy, and adherence to a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-based antiretroviral therapy regimen.

Conclusions: CVD risk in PLHIV is dynamic and modifiable. The use of NNRTI-based regimens and lipid-lowering therapies contributed to a significant risk reduction. Comprehensive integrated management strategies addressing both HIV infection and cardiovascular health are essential. Further research is needed on the cardiovascular effects of integrase inhibitors (INSTIs), particularly their long-term effects on lipid profiles and endothelial function.

Keywords: cardiovascular disease, HIV, integrase inhibitors, lipid profile, prospective study, risk factors

Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality among adults living with HIV (PLHIV). It accounts for approximately 13% of all non-AIDS-related deaths in this population (Farahani et al., 2017). Compared with HIV-negative individuals, PLHIV are 1.5 to 2 times more likely to develop heart disease, and this risk increases with age. Previous cross-sectional studies have estimated that 1.7%–34.7% of PLHIV may face an elevated risk of CVD in the next decade (Kim SunBean et al., 2013; Nery et al., 2013; Begovac et al., 2015; Kingery et al., 2016; Krikke et al., 2016; Muyanja et al., 2016; Mosepele et al., 2017).

However, many of these studies relied on risk assessment tools designed for the general population, which may not fully capture HIV-specific factors. The data collection on adverse events of anti-HIV drug (D:A:D) model is the only validated risk prediction tool that incorporates both conventional CVD risk factors and exposure to combination antiretroviral therapy (cART) (Triant et al., 2018; Friis-Møller et al., 2016). It has been shown to reliably estimate the 5-year probability of CVD,

myocardial infarction (MI), and coronary heart disease (CHD) in PLHIV (Krikke et al., 2016).

Previous studies have found that changes in blood pressure (BP) and cholesterol levels are strongly associated with an increased risk of CVD and MI (Diaz et al., 2014; Ye et al., 2014; Smit et al., 2018). In particular, alterations in lipid profiles and BP significantly contribute to the incidence of CVD and MI events (Buchacz et al., 2008; Hanna et al., 2016; Kent et al., 2016; Zhou et al., 2016). It is also well recognized that certain antiretroviral drugs, such as stavudine and protease inhibitors (PIs), exert stronger adverse effects on lipid metabolism than other regimens (Bavinger et al., 2013; Dillon et al., 2013; Jamieson et al., 2017). Switching from one regimen to a more "lipid-friendly" therapy may improve lipid parameters and lower the estimated CVD risk (Price et al., 2015; Rokx et al., 2015).

The temporal variability of CVD risk in PLHIV has only been explored in a few studies. Findings from the D:A:D cohort showed that after seven years, the proportion of patients with a high CVD risk (D:A:D score >5%) remained high, at 47.8% in men and 20.4%–22.9% in women (Sabin et al., 2013). Another study reported that treatment-naïve patients had increased CVD risk that persisted during the first year of cART as measured by impaired brachial artery flow-mediated vasodilation (Maggi et al., 2017). In contrast, other studies have found no significant change in long-term CVD risk over 10 years (Price et al., 2015; Maggi et al., 2017). These conflicting findings highlight the need to better understand why CVD risk profiles change over time, and how such changes influence the development of clinical events.

Traditional CVD risk factors, such as smoking, hypertension, and diabetes, are more prevalent among PLHIV, and HIV-related chronic inflammation and immune activation add to this risk (Hsue & Tawakol, 2016; Vos et al., 2016). Moreover, cART regimens may influence cardiovascular outcomes (D'Ascenzo et al., 2012; Islam et al., 2019).

The role of immunological status, particularly the CD4 cell count, remains controversial. Some studies have shown that lower CD4 counts are associated with a higher CVD risk, whereas others have reported no relationship. For example, the D:A:D study reported that individuals with CD4 counts <500 cells/μL experienced higher CVD event rates (Lichtenstein et al., 2010), a 10-year analysis failed to confirm this association with MI or CHD. Similarly, several meta-analyses have identified elevated CVD risk with overall antiretroviral therapy use, but evidence linking specific regimens to CVD remains mixed (Cruciani et al., 2011). Some studies found a strong association between PI use, particularly abacavir, and increased CVD risk (Cruciani et al., 2011), whereas others, such as the Swiss HIV cohort, reported no such relationship.

Given these uncertainties, further investigation of short- and long-term changes in CVD risk among PLHIV is warranted. Therefore, this study applied the updated D:A:D prediction model to assess changes in the 5-year estimated CVD risk and associated factors over a 12-month follow-up period (Friis-Møller et al., 2016).

Materials and Methods

Study design and subjects

This prospective study was conducted from July 2016 to February 2018 at a university-affiliated hospital in southern Taiwan, specializing in HIV care. The hospital provided HIV services for over 30 years, caring for more than 2,000 patients in 2016, with a demographic distribution comparable to the 30,625 cases reported by the Taiwan Centers for Disease Control. Eligible participants were adults (≥18 years) living with HIV and not currently receiving cardiovascular medications. Pregnant women were excluded from this study. The participants were monitored at three time points: baseline (T0), 6 months (T1), and 12 months (T2). A total of 411 individuals were enrolled, but only 51.3% completed the 12-month follow-up period.

Measures

The updated D:A:D risk prediction models (full and reduced) were used to estimate 5-year CVD risk (Friis-Møller et al., 2016). The complete model included 13 variables: (1) age, (2) sex, (3) family history of CVD, (4) diabetes mellitus, (5) systolic blood pressure, (6) current smoking, (7) smoking history, (8) total cholesterol, (9) HDL cholesterol, (10) CD4 cell count, (11) use of abacavir, (12) duration of exposure to protease inhibitors (PIs), and (13) duration of exposure to nucleoside reverse transcriptase inhibitors (NRTIs). Risk was categorized as low (<1%), moderate (1–5%), high (6–10%), or very high (>10%) over 5 years.

Vital signs included blood pressure (measured twice consecutively with a calibrated digital sphygmomanometer and averaged), heart rate, weight, height, and body mass index (BMI). Hypertension was defined as blood pressure ≥140/90 mmHg (Pickering, 2007).

CD4 and viral loads were measured at baseline, 6 months, and 12 months using routine hospital laboratory protocols aligned with national HIV monitoring standards.

Laboratory tests included lipid profiling (triglycerides, total cholesterol [TC], low-density lipoprotein [LDL], and high-density lipoprotein [HDL]). Abnormal cutoffs were defined as TC ≥200 mg/dL, LDL ≥100 mg/dL, triglycerides ≥150 mg/dL, and HDL < 40 mg/dL (Rodbard et al., 2007).

Medical records provided additional details on the HIV diagnosis date, ART regimen and duration, abacavir

or lopinavir use, co-infections (hepatitis B and C), and cardiovascular medication use.

Demographics and health behaviors (age, sex, education, marital status, occupation, smoking history, HIV transmission risk factors, family history of CVD, and comorbidities) were collected using standardized electronic forms.

Procedure

All the participants provided written informed consent. This study was approved by the hospital's Institutional Review Board (ER-98-090). The participants were evaluated during routine HIV clinic visits at T0, T1, and T2. Data were obtained through physical examination, structured interviews, and a review of electronic medical records. The case managers referred eligible patients to the research team to ensure continuous recruitment and follow-up.

Data analysis

Descriptive statistics were used to summarize sociodemographic and clinical characteristics. Baseline differences between completers and non-completers and among CVD risk categories were assessed using the chi-square test and one-way ANOVA. Repeated-measures ANOVA with Bonferroni correction was used to compare the mean risk scores across T0, T1, and T2. For paired changes in the multi-category CVD risk groups between baseline and 12 months, we applied the McNemar–Bowker (Stuart–Maxwell) test. To account for repeated measures and potential dropout bias, linear mixed-effects models, with patient ID as a random effect, were applied. Missing data from dropouts were handled using maximum likelihood estimation under the assumption of missing at random (MAR), which allows unbiased estimation in longitudinal analyses. Model fit was assessed using intraclass correlation coefficients (ICC), −2 log likelihood, and Akaike's Information Criterion (AIC). All statistical analyses were conducted using IBM SPSS version 23.0, and significance was set at $p < 0.05$.

Results

Demographics characteristics and HIV-related information

A total of 411 people living with HIV participated in the study. Of these, 335 individuals (81.5%) completed the 6-month follow-up assessment and 211 (51.3%) completed the 12-month assessment. Table 1 shows significant differences in baseline characteristics across the 5-year predicted cardiovascular disease (CVD) risk groups. Mean age increased progressively from the low-risk group (29.0 ± 5.7 years) to the very high-risk group (58.0 ± 3.2 years) ($p < 0.001$, trend). The proportion of participants with ≥12 years of education declined from 45.6% in the low-risk group to 11.1% in the high- and very-high-risk groups ($p < 0.001$). Sex and marital status did not differ significantly between groups. CD4 cell counts were lower in the very high-risk group (374 ± 283 cells/mm³) than in the low-risk group (497 ± 240 cells/mm³) ($p = 0.005$), while the mean log viral load was highest in the very high-risk group (5.3 ± 3.8; $p = 0.005$). Hepatitis C co-infection increased with a higher CVD risk (0.5% in the low-risk group vs. 13.3% in the high-risk group and 11.1% in the very high-risk group; $p = 0.003$). Lopinavir use was more frequent in the high-risk group (7.8% vs. 24.4%; $p = 0.008$). Current smoking increased from 38.3% in the low-risk group to 100% in the high-risk group ($P < 0.001$). Diabetes mellitus (0.5% vs. 33.3%; $p < 0.001$), BMI ≥ 25 kg/m² (14.0% vs. 33.3%; $p = 0.017$), hypertension (14.5% vs. 27.8%; $p = 0.004$), and dyslipidemia was more prevalent in the high-risk group. Moreover, lipid-lowering therapy (2.1% vs. 22.2%; $p < 0.001$) and BP-lowering therapy (4.1% vs. 22.2%; $p = 0.010$) increased the risk of CVD.

Estimation of CVD risk at baseline

The analytical findings obtained using the simplified D: A:D model are presented in Table 1. In the five years that followed, 47% of participants were at low risk of CVD, 37.7% were at moderate risk, 10.9% were at high risk, and 4.5% were at very high risk, according to the data. The CVD risk classification was broadly similar using the reduced and full D:A:D models.

In this cohort, higher predicted CVD risk categories were characterized by older age, current smoking, diabetes mellitus, overweight/obesity (BMI ≥25 kg/m²), elevated blood pressure (≥140/90 mmHg), and less favorable lipid profiles, including total cholesterol ≥200 mg/dL, triglycerides ≥150 mg/dL, HDL <40 mg/dL, and LDL ≥100 mg/dL. Lower educational attainment was also more common in high-risk categories. HIV-related factors, such as lower CD4 count, higher viral load, HCV co-infection, and use of specific ART agents (e.g., lopinavir and abacavir), were more prevalent in the very high-risk group at baseline (Table 1).

Change in CVD risk overtime

Figure 1 depicts the shifts in the 5-year predicted CVD risk categories based on the reduced D:A:D model, comparing changes from T1 to T2 and from T0 to T2. Overall, a greater proportion of participants moved to lower-risk categories than to higher-risk categories, driven mainly by transitions to the low-risk group (−7.8% from T1 to T2 and −8.1% from T0 to T2) and moderate-risk group (−2.9% and −3.8%, respectively). Upward transitions were smaller, including increases in the moderate-risk group (+3.4% and +4.3%), high-risk group (+3.4% and +1.9%), and very high-risk group (+1.5% and +0.9%). These findings indicate that the CVD risk classification in this cohort changed over time, with net movement toward a lower predicted risk across follow-up.

Table 1. Comparison of frequency distributions of demographic data, HIV-related information, and traditional CVD risk factors based on CVD risk groups at baseline (N=411). (Numbers in parentheses are percentages unless otherwise specified)

Variables	Total (n = 411)	Low risk <1% (n = 193)	Moderate risk 1–5% (n = 155)	High risk 6–10% (n = 45)	Very high risk >10% (n = 18)	p-value
Age (years), mean ± SD	38.0 ± 12.0	29.0 ± 5.7	43.2 ± 8.2	52.0 ± 5.9	58.0 ± 3.2	<0.001[a]
≤30 years	123 (29.9)	117 (60.6)	5 (3.2)	0 (0.0)	1 (5.6)	<0.001[a]
30–45 years	170 (41.4)	75 (38.9)	93 (60.0)	2 (4.4)	0 (0.0)	
45–59 years	98 (23.8)	1 (0.5)	50 (32.3)	39 (86.7)	8 (44.4)	
≥60 years	20 (4.9)	0 (0.0)	7 (4.5)	4 (8.9)	9 (50.0)	
Male sex	394 (95.9)	188 (97.4)	145 (93.5)	44 (97.8)	17 (94.4)	0.288
Unmarried	244 (59.4)	114 (59.1)	93 (60.0)	26 (57.8)	11 (61.1)	0.507
≥12 years of education	150 (36.5)	88 (45.6)	55 (35.5)	5 (11.1)	2 (11.1)	<0.001[a]
HIV risk factors†						0.304
Heterosexual	62 (15.1)	32 (16.6)	25 (16.1)	3 (6.7)	2 (11.1)	
Injecting drug use	59 (14.4)	30 (15.5)	20 (12.9)	5 (11.1)	4 (22.2)	
MSM	150 (36.5)	60 (31.1)	64 (41.3)	20 (44.4)	6 (33.3)	
Unknown/others	11 (2.7)	8 (4.1)	2 (1.3)	1 (2.2)	0 (0.0)	
CD4 count (cells/mm³), mean ± SD	523 ± 256	497 ± 240	560 ± 274	572 ± 214	374 ± 283	0.005
Ln viral load, mean ± SD	4.5 ± 3.1	5.0 ± 3.4	4.0 ± 2.6	3.8 ± 2.3	5.3 ± 3.8	0.005
HIV duration (years), mean ± SD	9.2 ± 7.2	10.1 ± 7.9	8.9 ± 6.7	7.1 ± 5.1	6.9 ± 6.2	0.030
Co-infection						
Hepatitis B	54 (13.1)	16 (8.3)	28 (18.1)	7 (15.6)	3 (16.7)	0.043
Hepatitis C	21 (5.1)	1 (0.5)	12 (7.7)	6 (13.3)	2 (11.1)	0.003
ART regimen						0.001
No ART	15 (3.6)	12 (6.2)	2 (1.3)	1 (2.2)	0 (0.0)	
II-based	48 (11.7)	20 (10.4)	20 (12.9)	6 (13.3)	2 (11.1)	
NNRTI-based	212 (51.6)	114 (59.1)	69 (44.5)	21 (46.7)	8 (44.4)	
PI-based	103 (25.1)	41 (21.2)	47 (30.3)	12 (26.7)	3 (16.7)	
Other combinations	13 (3.2)	1 (0.5)	8 (5.2)	1 (2.2)	3 (16.7)	
Lopinavir use	53 (12.9)	15 (7.8)	23 (14.8)	11 (24.4)	4 (22.2)	0.008
Abacavir use	87 (21.2)	32 (16.6)	39 (25.2)	13 (28.9)	3 (16.7)	0.125
ART duration (years), mean ± SD	8.7 ± 6.6	10.0 ± 7.2	7.8 ± 6.0	5.6 ± 4.4	6.5 ± 4.4	<0.001
Traditional CVD risk factors						
Current smoker	231 (56.2)	74 (38.3)	99 (63.9)	40 (88.9)	18 (100.0)	<0.001[a]
Diabetes mellitus	17 (4.1)	1 (0.5)	7 (4.5)	3 (6.7)	6 (33.3)	<0.001
BMI ≥25 kg/m²	81 (19.7)	27 (14.0)	34 (21.9)	14 (31.1)	6 (33.3)	0.017
BP ≥140/90 mmHg	82 (19.9)	28 (14.5)	33 (21.3)	16 (35.6)	5 (27.8)	0.004
Family history of CVD	194 (48)	79 (42)	77 (50)	28 (62)	10 (63.0)	0.041
Diabetes mellitus	17 (4)	1 (1)	7 (5)	3 (7)	6 (33.0)	<0.001
TC ≥ 200 mg/dl	72 (17)	14 (7)	35 (23)	18 (40)	5 (28.0)	<0.001
HDL < 40 mg/dl	164 (40)	74 (39)	61 (39)	17 (38)	12 (67.0)	0.137
TG ≥150 mg/dl	137 (33)	32 (17)	69 (45)	24 (53)	12 (67.0)	<0.001
LDL ≥ 100 mg/dl	219 (53)	82 (43)	91 (59)	36 (80)	10 (56.0)	<0.001
Lipid-lowering therapy	32 (7.8)	4 (2.1)	13 (8.4)	11 (24.4)	4 (22.2)	<0.001
BP-lowering therapy	32 (7.8)	8 (4.1)	12 (7.7)	8 (17.8)	4 (22.2)	0.010

Data are presented as the mean ± SD or n (%). Continuous variables were compared using ANOVA or Kruskal–Wallis tests, as appropriate; categorical variables were analyzed using Chi-square or Fisher's exact tests when expected cell counts were <5. [a] Trend test was applied for ordered categorical variables. † Participants could report more than one HIV transmission risk factor. ART, antiretroviral therapy; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HDL, high-density lipoprotein; II, integrase inhibitor; LDL, low-density lipoprotein; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TC, total cholesterol; TG, triglycerides; VL, viral load.

Figure 2 presents the changes in the prevalence of modifiable CVD risk factors between baseline (T0) and 12-month follow-up (T2). Significant reductions were observed in current smoking (−5.0%), total cholesterol ≥200 mg/dL (−3.4%), HDL cholesterol <40 mg/dL (−4.8%), and abacavir use (−7.3%) (McNemar–Bowker test, $p < 0.05$). In contrast, a significant increase was noted in the proportion of participants with CD4 counts of >500 cells/μL (+7.1%, $p < 0.05$). Smaller, non-significant changes were observed for diabetes mellitus (−0.3%), BMI ≥25 kg/m² (+2.3%), and blood pressure ≥140/90 mm Hg (−0.8%). Overall, these findings suggest an improvement in several key modifiable risk factors during the follow-up period.

Predictors of full and reduced D: A: D model

We used linear mixed-effect models with a random effect of patients to identify factors that were linked with a lower D:A:D risk score. According to the interclass correlation (ICC), decreased D: A: D accounted for 43.3% of the variance. The model's fixed- and random-effects tests indicated that the intercept was statistically significant. A -2 log likelihood of 375.67 and an AIC of 401.67, indicated that the model was well fitting.

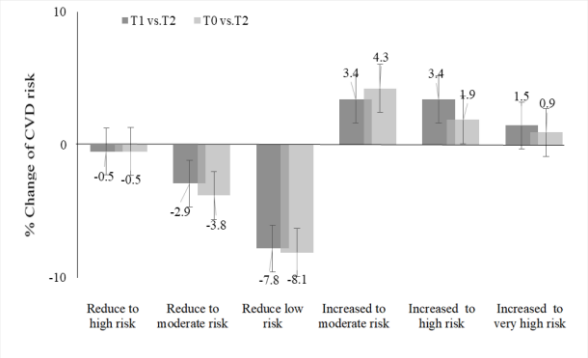

Figure 1. Change of 5-years cardiovascular risk from T1 to T2 and T0 to T2 based on reduced D: A: D model.

Note: Reduced to high risk "Reduced to high risk" indicates movement from very high to high; "Reduced to moderate risk" indicates very high/high to moderate; "Reduced to low risk" indicates very high/high/moderate to low; "Increased to moderate risk" indicates low to moderate; "Increased to high risk" indicates low/moderate to high; and "Increased to very high risk" indicates low, moderate, high, and very high.

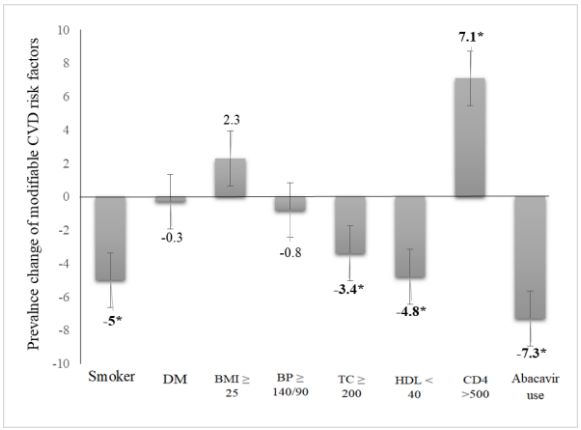

Figure 2. Changes in the prevalence of modifiable CVD risk factors among HIV-positive individuals from baseline (T0) to the 12-month follow-up (T2), based on the reduced D:A:D CVD risk prediction model.

*Bold values indicate p<0.05 (McNemar–Bowker test). Abacavir use is a component of the D:A:D full model and is shown here for comparison. Abbreviations: BP, blood pressure; BMI, body mass index; DM, diabetes mellitus; HDL, high-density lipoprotein; TC, total cholesterol.

In the reduced model, time was not significantly associated with changes in the D:A:D score (β = −0.03; 95% CI −0.47 to 0.41). Higher educational attainment was independently associated with a lower D:A:D score (β = −1.79; 95% CI −2.63, −0.95), whereas increasing age (ln-transformed) showed a strong positive association (β = 5.73; 95% CI 5.09 to 6.37). Traditional cardiovascular risk factors were significant predictors of higher D:A:D scores, including diabetes mellitus (Î ² = 3.75; 95% CI 2.57 to 4.93), current smoking (Î ² = 2.50; 95% CI 1.91 to 3.09), higher total cholesterol (Î ² = 2.04; 95% CI 0.92 to 3.16),

Table 2. Linear mixed effect models for predictors of full and reduced D: A: D model

Factors[a]	Full D:A: D model Coeff. (95% CI)	Reduced D:A:D Coeff. (95% CI)
Fixed effects		
Time (No. months)	0.10 (−0.34, 0.54)	−0.03 (−0.47, 0.41)
Socio-demographic		
Married (vs. unmarried)	−0.81 (−2.24, 0.62)	−0.84 (−2.19, 0.51)
High education (vs. low)	−2.36* (−3.28, −1.43)	−1.79* (−2.63, −0.95)
CVD risk factors		
Ln age	6.29* (5.60, 6.98)	5.73* (5.09, 6.37)
Male (vs. female)	0.94 (−0.24, 2.12)	1.00 (−0.08, 2.09)
Diabetic mellitus (yes/no)	4.19* (2.91, 5.47)	3.75* (2.57, 4.93)
Family history of CVD (yes/no)	0.23 (−0.29, 0.75)	0.35 (−0.13, 0.84)
Current Smoker (yes/no)	2.99* (2.34, 3.63)	2.50* (1.91, 3.09)
Previous smoker (yes/no)	−0.62 (−1.32, 0.09)	−0.26 (−0.92, 0.39)
Ln total cholesterol (mg/dl)	2.00* (0.80, 3.22)	2.04* (0.92, 3.16)
Ln HDL (mg/dl)	−2.50* (−3.38, −1.60)	−2.28* (−3.09, −1.46)
Ln SBP (mmHg)	4.91* (2.52, 7.31)	3.64* (1.42, 5.89)
Lipid-lowering drugs (yes/no)	−2.75* (−4.04, −1.46)	−1.94* (−3.07, −0.81)
BP-lowering drugs (yes/no)	−2.64* (−3.86, −1.41)	−2.62* (−3.70, −1.55)
ART-related treatment		
Duration of ART (no. years)	−0.09* (−0.14, −0.04)	−0.11* (−0.17, −0.07)
Use of II-based (yes/no)	−1.14 (−2.29, 0.02)	−0.57 (−1.79, 0.64)
Use of NNRTI-based (yes/no)	−1.89* (−2.29, −1.12)	−1.09* (−1.92, −0.27)
Use of Abacavir (yes/no)	3.42* (2.45, 4.38)	1.48* (0.59, 2.36)
Abacavir exposure (no.years)	0.35* (0.11, 0.58)	0.13 (−0.08, 0.34)
Use of Lopinavir(yes/no)	3.19* (2.14, 4.24)	1.41* (0.35, 2.47)
Lopinavir exposure (no. years)	0.58* (0.19, 0.96)	0.31* (0.08, 0.53)
HIV-related factors		
Ln2 CD4 cell count (cells/mm3)	−0.27 (−0.75, 0.22)	−0.09 (−0.54, 0.34)
Ln viral load (copies/ml)	−0.15 (−0.38, 0.07)	0.14 (−0.32, 0.60)
Hepatitis B (yes/no)	1.02 (−0.86, 2.90)	0.71 (−0.84, 2.27)
Hepatitis C (yes/no)	3.23* (0.75, 5.71)	2.88* (0.83, 4.94)
Years living with HIV	−0.05 (−0.15, 0.05)	−0.09 (−0.19, 0.01)
MSM (yes/no)	0.87 (−0.98, 2.72)	0.91 (−0.63, 2.44)
Injecting drug users (yes/no)	0.61 (−1.43, 2.64)	0.93 (−0.75, 2.61)
Heterosexual(yes/no)	−0.83 (−1.98, 0.31)	−0.99* (−1.97, −0.02)
Unknown	0.14 (−3.91, 4.17)	0.11 (−3.24, 3.45)

Noted; *p<0.05;[a] Variable in brackets is the reference category for independent variables; ART: antiretroviral therapy; BP: blood pressure; BMI; body mass index; CVD: cardivascular disease; D:A:D= data-collection on adverse effects of anti-HIV drugs; HDL: high density lipoprotein; II: integrase inhibitors; LDL: low density lipoprotein; Ln: log; Ln2: log base 2; NNRTI: Non-nucleoside reverse transcriptase inhibitors; MSM: men who have sex with men PI: protease inhibitors; TC: total cholesterol, TG: triglyceride; VL: viral load.

and higher systolic blood pressure ($\hat{I}^2$ = 3.64; 95% CI 1.42 to 5.89). In contrast, higher HDL cholesterol levels were associated with a lower D:A:D score (β = −2.28; 95% CI −3.09 to −1.46). Use of lipid-lowering (β = −1.94; 95% CI −3.07 to −0.81) and blood pressure-lowering therapy (β = −2.62; 95% CI −3.70 to −1.55) was independently associated with reduced D:A:D risk. ART-related factors also contributed significantly: a longer duration of ART was associated with a lower D:A:D score (β = −0.11; 95% CI −0.17, −0.07), and the use of an NNRTI-based regimen remained protective (β = −1.09; 95% CI −1.92, −0.27). Conversely, abacavir use (β = 1.48; 95% CI 0.59 to 2.36) and lopinavir use (β = 1.41; 95% CI 0.35 to 2.47) were associated with higher D:A:D scores, with additional risk observed with longer lopinavir exposure (β = 0.31; 95% CI 0.08 to 0.53). Among HIV-related factors, hepatitis C co-infection was independently associated with an increased D:A:D risk (β = 2.88; 95% CI 0.83 to 4.94), whereas CD4 cell count, viral load, and years living with HIV were not significantly associated with the D:A:D score in the adjusted model. Heterosexual transmission was associated with a lower D:A:D score than other transmission categories (β = −0.99; 95% CI −1.97, −0.02) (Table 2).

Discussions

According to the reduced D:A:D model, approximately 15.3% of this relatively young cohort of adults living with a stable HIV infection who received ART had a projected high or very high 5-year CVD risk (Furuya-Kanamori, Kelly, & McKenzie, 2015; Krikke et al., 2016; Thompson-Paul et al., 2016). Compared with earlier work in Queensland, where 47% of participants were categorized as high-risk (Edwards-Jackson et al., 2011; Mashinya et al., 2015), our findings suggest a lower trend. In contrast, when compared with studies from South Africa (4.2% high or very high risk) and Thailand (0.8% high risk), the prevalence in our cohort was higher. These variations likely reflect differences in the age distribution, ART coverage, and study methodology. Because our respondents were younger, had shorter durations of HIV infection, and were more frequently on ART than non-respondents, the overall risk in our study may have underestimated the true CVD burden in this population.

Importantly, results from the linear mixed-effects model demonstrated that time itself was not independently associated with changes in the D:A:D risk score, indicating no significant temporal increase or decrease in the predicted CVD risk over the follow-up period after adjustment for covariates. This finding contrasts with some earlier longitudinal studies reporting increased CVD risk over time; however, (Price *et al.*, 2015). the results may not be directly comparable because those studies used different prediction tools, had different follow-up times (every three months or six months with a duration ranging from one to seven years), and had different participant characteristics (mostly participants were over 30 years old and one study included ART-naïve participants).

Following the decrease in cardiovascular disease risk in our cohort, we found a decrease in the proportion of HIV-positive smokers, blood cholesterol levels (TC) ≥ 200 mg/dl, low HDL levels (<40 mg/dl), and an increase in the number of individuals with CD4 cell counts greater than 500 cell/mm3. In addition, a lower D:A:D risk score was strongly associated with interventions such as cholesterol- and BP-lowering treatments. In our study, a small percentage of the participants received lipid medications, and a similar percentage did not stop, even though this evidence was present. Less than 20% of those who tried to discontinue using proven medicines and even fewer who were HIV positive and receiving antiretroviral therapy actually started using statins, according to previous research(Cui *et al.*, 2010; Chew *et al.*, 2014; Vijayaraghavan *et al.*, 2014). One essential method for preventing cardiovascular disease is to encourage people to stop smoking and start taking statins if they are on antiretroviral therapy (ART) for an extended period. This had a positive effect on lipid metabolism.

The D:A:D risk score was higher in patients with hepatitis C infection. According to a pooled meta-analysis, the risk of cardiovascular disease (CVD) is 1.24 to 1.33 times higher in people with hepatitis B and HIV monoinfection,(Osibogun *et al.*, 2017) compared to individuals with HIV or hepatitis C monoinfection as well as healthy controls. Those with hepatitis C co-infection had significantly lower lipid levels and increased endothelial markers (Kakinami *et al.*, 2013). It is not yet known how hepatitis C co-infection increases the risk of cardiovascular disease (CVD), whether the two viruses work together to cause CVD, or whether the effects of CVD are independent of hepatitis C co-infection (Mehta *et al.*, 2000; McKibben *et al.*, 2016; Osibogun *et al.*, 2018). Consistent with other studies(Butt *et al.*, 2009; Adinolfi *et al.*, 2013), our results suggest that co-infection with hepatitis C independently increases the risk of cardiovascular disease. Age, proportion of former smokers, and ART exposure regimen were the only CVD risk variables that showed statistically significant differences between our cohort and the non-hepatitis C group (Table S2). Further long-term research is needed to understand how chronic hepatitis C infection causes cardiovascular diseases.

The use of Lopinavir and Abacavir significantly increased the D:A:D risk scores. According to a prior meta-analysis, some antiretroviral medications, including Abacavir, Indinavir, and Lopinavir, may increase the risk of cardiovascular disease (Cruciani *et al.*, 2011; D'Ascenzo *et al.*, 2012). Consistent with earlier findings, PIs had a more substantial effect on impairment of lipid metabolism. Our investigation revealed that PI consumers had significantly higher TG, LDL, and HDL levels. Our data suggest that regimens based on NNRTIs can help protect against cardiovascular diseases. In contrast to PIs and NRTIs, prior research has shown that

the majority of NNRTs have no effect on metabolic profiles and a low relative risk of CVD events (Kaplan-Lewis, Aberg and Lee, 2016). The complicated influence of antiretroviral therapy (ART) on cardiovascular risk is due to the fact that many patients have undergone many regimens, and that the typical ART regimen includes at least three drugs from two pharmacological groups. Further studies on the influence of these drugs on CVD risk are needed, and healthcare providers should be cautious when administering integrase strand transfer inhibitors (INSTIs) and other antiretroviral therapy (ART) regimens that increase the risk of CVD.

This study had several limitations. First, nearly half of the participants (48.7%) did not complete the 12-month follow-up, which may have introduced an attrition bias. Although mixed-effects models were used to account for missing data, individuals who dropped out may have had different risk profiles than those retained, potentially leading to underestimation or overestimation of the CVD risk. Second, our sample was predominantly male (93.9%), limiting the ability to generalize the findings to women living with HIV who may experience distinct cardiovascular risk patterns. Third, participants in our study were younger, had shorter durations of HIV infection, and were more likely to receive ART than non-respondents. These characteristics may underestimate the long-term CVD risk in this population. Fourth, data on several important behavioral factors, including diet, physical activity, and psychosocial stress, were not systematically collected, preventing us from fully exploring their impact on CVD risk. Finally, the study was conducted at a single university-affiliated hospital in Southern Taiwan. Therefore, the findings may not be generalizable to other HIV populations in Taiwan or in different geographic and cultural contexts, particularly in low- and middle-income countries with different treatment infrastructure and sociodemographic characteristics.

Conclusion

Our findings indicate that while the overall projected 5-year CVD risk among Taiwanese adults living with HIV was lower than that in some international cohorts, it was still higher than that reported in several regional studies. Increased D:A:D risk scores were associated with older age, traditional cardiovascular risk factors, hepatitis C co-infection, and use of lopinavir- or abacavir-based regimens, whereas risk reduction was linked to NNRTI-based therapy, longer ART duration, and use of lipid-lowering medications. This highlights the need to integrate comprehensive cardiovascular risk assessment and management into routine HIV care, expand access to statins and antihypertensive therapy, and carefully balance virological efficacy with long-term cardiovascular safety when selecting ART regimens. Developing coordinated national strategies for simultaneous HIV and CVD management is essential to reduce the future cardiovascular burden in this population.

Acknowledgments

National Cheng Kung University Hospital provided funding for this research.

Funding source

The authors would like to express their sincere appreciation to the staff and patients of the designated AIDS treatment center at National Cheng Kung University Hospital for their participation and support. Special thanks are extended to the case managers and medical record officers who facilitated data collection and access. We also acknowledge the contribution of the research assistants involved in participant recruitment and follow-up.

Authors' contributions

LL: conception and design of the study, data collection, data analysis and interpretation, and drafting of the manuscript. The author also took a lead role in revising the manuscript critically for important intellectual content and approved the final version for submission; YL: development of the research methodology, data collection process, and critical review of the manuscript; WCK: data analysis and interpretation, contributed to drafting the results and discussion sections, and participated in revising the manuscript for intellectual content and coherence.; JDW: data analysis and interpretation, contributed to drafting the results and discussion sections, and participated in revising the manuscript for intellectual content and coherence; NYK: data analysis and interpretation, contributed to drafting the results and discussion sections, and participated in revising the manuscript for intellectual content and coherence.

Declaration of Interest

The authors have no conflicts of interest.

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How to cite this article: Lindayani, L., Lai, Y., Ko, W. C., Wang, J. D., and Ko, N. Y. (2026) 'Change in Cardiovascular Risk Profile in People with Human Immunodeficiency Virus Infection: A-12 Months Follow Up', *Jurnal Ners*, 21(1), pp. 67-75. doi: http://dx.doi.org/10.20473/jn.v21i1.72933