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# Intensive statin regimens for reducing risk of cardiovascular diseases among human immunodeficiency virus-infected population: A nation-wide longitudinal cohort study 2000–2011

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ABSTRACT

*Objective:* This study evaluated the risk of cardiovascular diseases (CVD) in a statin-treated HIV-infected population and the effects of intensive statin regimens (i.e., high-dose or potency) on CVD risks.
*Methods:* 945 HIV-infected patients newly on statin treatment (144, 15.7% with CVD history) were identified from Taiwan's national HIV cohort. Using the median of the first year cumulative statin dosage as a cut-off point, patients were classified into either a high-dose or low-dose group. Patients were also classified as high-potency (i.e., atorvastatin) or low-potency (i.e., pravastatin) statin users. CVD, including ischemic stroke, coronary artery diseases, and heart failure, were identified after statin use to the end of 2011. Cox hazards regression was applied to assess the time-to-event hazards of CVD in association with intensive statin regimens.
*Results:* In the HIV-infected population with CVD history, the high-dose group had a lower CVD risk compared to that of the low-dose group (hazard ratio [HR]: 0.88, 95% confidence interval [CI]: 0.39–1.99). The high-potency group showed a lower CVD risk compared to that of the low-potency group (HR: 0.42, 95% CI: 0.06–3.13). For those without CVD history, the corresponding figures were HR: 0.64 (95% CI: 0.30–1.35) and HR: 0.67 (95% CI: 0.16–2.87). The event rate of new-onset diabetes in high-dose statin group was higher than that in low-dose statin group (15.28% vs. 8.33%), while no muscle complications (i.e., myalgia, myositis, rhabdomyolysis) and dementia were observed in statin users.
*Conclusions:* There appears a trend showing a lower CVD risk in HIV patients receiving intensive statin therapy.


## 1. Introduction

People living with human immunodeficiency virus (HIV) infection are at 50%–80% higher risk of developing cardiovascular disease (CVD) compared to that for the uninfected population [1]. In the United States, CVD has become a common cause of death in HIV patients; proportionate mortality due to CVD in HIV patients increased significantly from 1999 to 2013 ($p < 0.0001$) [2]. Current data of CVD event rates among HIV-infected patients are mostly from the United States [3–7], Canada [8], and European countries [9,10], with a lack of such evidence from Asia [11].

The pathogeneses of CVD in HIV patients are complex; several conventional factors (e.g., smoking) and HIV related factors (e.g., HIV infection, HIV medications) can alter lipid homeostasis, contributing to excess risk of CVD [11]. HIV infection, by itself, can cause lipid changes (e.g., elevated LDL-C, lower HLD levels) [12–15]. Also, HIV co-infections — frequent hepatitis C infection that damage liver and pancreas may further exacerbate glucose and lipid abnormalities. Moreover, antiretroviral therapy (ART) could induce considerable metabolic complications of lipid metabolism, including lipodystrophy, central adiposity, and dyslipidemia [12,13,16,17]. The high prevalence of dyslipidemia, marked with increased serum triglyceride (TG) and impaired high density lipoprotein- cholesterol (HDL-C) functions (i.e., decreased cholesterol efflux, anti-inflammatory, and antioxidative) has been observed among 176 HIV patients from cardiovascular sub-study of the CARE [18], and these lipid markers were significant contributors in carotid thickening.

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Statins are a class of drugs that have been demonstrated to be effective in lowering the level of low-density lipoprotein-cholesterol (LDL-C) and the risk of CVD in non-HIV populations [19]. Intensive statin regimens (i.e., high-dose or high-potency statin) can produce a highly significant reduction in CVD risks compared to that obtained with less intensive ones in non-HIV populations [19]. In HIV-infected population, an estimated 20% of the patients are currently taking statins to control their cholesterol levels [1]. However, there is uncertainty as to whether statin can reduce CVD risk in HIV patients [20–24], and data on CVD risk in the Asian HIV-infected population are scarce. We therefore conducted a cohort study based on a nation-wide longitudinal HIV cohort to evaluate CVD rates among HIV patients in Taiwan and to determine whether intensive statin regimens (i.e., high dose or potency) are associated with lower CVD risk in such individuals. Also, intensive therapy may increase risk for severe adverse events such as rhabdomyolysis [25]. So, the safety of intensive statin therapy is the secondary outcomes of interest.

## 2. Methods

### 2.1. Data source

We utilized a longitudinal national cohort of people living with HIV in the period 2000–2011 from the National Health Insurance Research Database (NHIRD), which is provided by Taiwan's National Health Research Institutes. Taiwan's NHIRD is population-based and derived from the claims data of the National Health Insurance program, a mandatory-enrollment, single-payment system that covers over 99% of population in Taiwan. The HIV cohort consists of 19,283 de-identified HIV-infected cases (confirmed by inpatient/ambulatory care files with the principal diagnosis of ICD-9 code = 042 or V08 and Case_Type = 91, which refers to HIV-infected cases that are reported for Taiwan Center for Disease Control (CDC) reimbursement) in the NHIRD for 2000–2011. This HIV cohort, due to it representativeness, provides an opportunity to evaluate long-term health outcomes associated with HIV [26]. The Institutional Review Board of National Cheng Kung University Hospital approved the study before commencement (B-ER-104-11).

### 2.2. Cohort and exposure to statins

From Taiwan's HIV cohort, we first identified 1135 patients who had initiated statin therapy after HIV diagnosis (Fig. 1). The date of the first statin prescription after HIV diagnosis during 2000–2009 was defined as the index date. In order to identify new users of statin, we excluded those who had used statin within one year before the index date. We identified a total of 915 HIV-infected patients newly on statin therapy from Taiwan's HIV cohort to form our study cohort. Statin users were stratified by CVD history before HIV diagnosis. 801 patients without CVD history and 144 patients with CVD history were identified. These groups of patients were analyzed separately.

The classification of active ingredients of drugs was based on the Anatomical Therapeutic Chemical (ATC) classification system. The ATC code for statins is "C10AA". Statins include lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, and rosuvastatin. The present study classified statin use in three ways: high- vs. low-dose statin, high- vs. low-potency statin, and adherence vs. non-adherence to statin use. First, statin users were classified into either high- or low-dose groups (two groups) based on the first-year cumulative statin dosage after the index date. The statin dosage was measured in terms of the defined daily dose (DDD), where for simvastatin, atorvastatin, pravastatin, fluvastatin, and lovastatin, 1 DDD = 15, 10, 20, 40, and 30 mg, respectively. The median of cumulative dose for HIV patients with CVD history was 150 DDD, while that for those without CVD history was 149 DDD (Fig. 1). For HIV patients without CVD history, statin users were also classified into high-, medium- or low-dose groups (three groups) based on tertiles cutoffs for cumulative statin dosage (i.e., 98 DDD, 210 DDD in Fig. 1). Second, statins were classified into high cholesterol-lowering efficacy/potency statins (atorvastatin and rosuvastatin) and low cholesterol-lowering efficacy/potency statins (pravastatin, fluvastatin, simvastatin, and lovastatin) [27]. Third, we computed the medication possession ratio (MPR) to estimate patients' adherence to statin. The MPR is defined as the number of days' supply of medication dispensed as a percentage of days of follow-up (capped at 100%). The patients were classified as either adherent (MPR ≥ 0.7) or non-adherent (MPR < 0.7) to statin treatment.

### 2.3. Study outcomes

The primary outcome of interest was a composite outcome of hospitalizations with diagnoses of ischemic stroke [ICD-9 CM: 430–438], coronary artery disease (CAD) [ICD-9 CM: 410–414], or heart failure [ICD-9 CM: 428] from NHIRD inpatient files. The secondary outcomes focused on the safety of intensive statin therapy to evaluate potential adverse events after the start of the therapy, including hospitalizations for muscle symptoms (i.e., myalgia [ICD-9 CM: 359.4, 359.5, 359.6, 359.8x x = 0~9, 359.9], myositis [ICD-9 CM: 729.1, 729.2, 729.5, 729.8x x = 0~9, 729.9], and rhabdomyolysis [ICD-9 CM: 728.88, 728.89, 791.3]), new-onset diabetes (i.e., at least 2 outpatient records of a diagnosis code of [ICD-9 CM: 250.0, 250.02], at least 1 outpatient record of diabetes code and at least 1 antidiabetic prescription, or at least 1 inpatient record of diabetes code within 1 year after index date [28]), and new-onset cognitive disorders (i.e., dementia) (i.e., at least 2 outpatient records of a diagnosis code of [ICD-9 CM: A210, A222, 290.0, 290.1, 294.1331.0–331.2, or 331.7–331.9], or at least 1 inpatient record of dementia within one year after index date [29]).

### 2.4. Study covariates

The analyses were adjusted for potential confounding factors, including patients' demographics (i.e., age and gender), HIV duration (from HIV diagnosis to the index date), comorbidity history from one year before the index date (i.e., hypertension, hyperlipidemia, diabetes, heart failure, stroke, and CAD), ART (i.e., nucleoside analog reverse-transcriptase inhibitors: NRTI; non-nucleoside reverse transcriptase inhibitors: NNRTI; and protease inhibitors: PI), and other medications related to CVD (i.e., angiotensin-II-

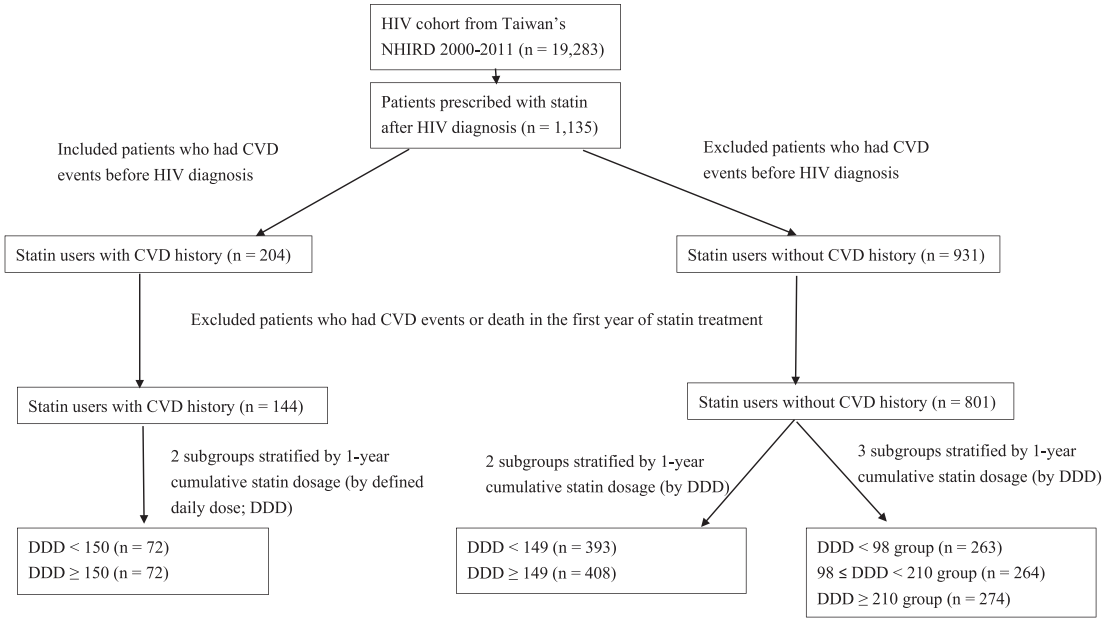


**Fig. 1.** Flow diagram of selection of study population. Abbreviations: NHIRD: National Health Institutes Research Database, HIV: human immunodeficiency virus, CVD: cardiovascular disease, DDD: defined daily dose.

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