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Dyslipidemia and cardiovascular disease in Vietnamese people with HIV on antiretroviral therapy

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Abstract: With expanding antiretroviral therapy (ART) in Vietnam, the use of second-line ART with ritonavir-boosted lopinavir (LPV/r) is increasing. However, little is known regarding the effect of LPV/r on dyslipidemia (DL) and cardiovascular disease (CVD) in people with HIV in Vietnam. A cross-sectional study was performed in a cohort of HIV-infected Vietnamese patients on ART at the National Hospital for Tropical Diseases in Hanoi, Vietnam. In addition to DL, we included hypertension (HT) and hyperglycemia (HG) as non-communicable diseases. Blood pressure, casual blood sugar levels, and the lipid profile were evaluated cross-sectionally in October and November 2016. The incidence of CVD was calculated in the cohort. We determined factors associated with diseases by univariate and multivariate analyses. A total of 1,346 subjects were evaluated for their non-communicable diseases. The subjects' mean age was 39.2 years and 41.8% were women. A total of 10.5% of the subjects had exposure to LPV/r. DL, HT, and HG was diagnosed in 53.5%, 24.4%, and 0.8% of the subjects, respectively. In multivariate analysis, age (OR = 1.040; 95% CI, 1.025-1.055), female sex (OR = 0.335; 95% CI, 0.264-0.424), and LPV/r exposure (OR = 3.251; 95% CI, 2.030-5.207) were significantly associated with DL. The incidence rate of CVD was 1.87/1,000 person-years (15 incidental cases in 8,013 person-years). LPV/r exposure was not a risk factor for the incidence of CVD. Although a causative relation with LPV/r and CVD was not identified in this study, attention should be paid to CVD for patients on LPV/r in the future.

***Keywords*:** dyslipidemia, cardiovascular disease, human immunodeficiency virus, Vietnamese, lopinavir-boosted ritonavir

Introduction

Cardiovascular disease (CVD) is becoming one of the major comorbidities in human immunodeficiency virus (HIV)-infected patients since widespread use of antiretroviral therapy (ART) has decreased AIDS-associated mortality (*1-3*). Some classes of antiretroviral drugs, such as protease inhibitors, can cause dyslipidemia (DL), which might lead to CVD (*4-7*). Among protease inhibitors, ritonavir-boosted lopinavir (LPV/r) is still a commonly used antiretroviral drug that World Health Organization guidelines recommend as the second-line salvage regimen in Vietnam (*8*). Lopinavir requires 200 mg of ritonavir as a booster and affects the lipid profile among various protease inhibitors. Recent studies have suggested that use of LPV/r is especially associated with CVD (*9,10*). The period of exposure to LPV/r has been increasing because of long-term survival of people living with HIV. Furthermore, there are situations that do not allow substitution of protease inhibitors to integrase inhibitors, which do not affect the lipid profile, in resource-limited settings because of budget limitations. The long-term effect of LPV/r on DL and CVD is of concern in this context.

Therefore, we conducted a cross-sectional study to evaluate the prevalence of DL and its associated factors. Furthermore, we performed a review of this cohort to estimate the incidence rate of CVD and causative relation between CVD and exposure to LPV/r in Vietnamese people living with HIV.

Materials and Methods

Study design

This study consisted of two parts, and was performed at the National Hospital for Tropical Disease, Hanoi, Vietnam. This hospital is one of the largest out-patient clinics for people with HIV in Vietnam. The study

population included Vietnamese people with HIV aged older than 17 years. In the first part of the study, we conducted a cross-sectional study to evaluate the prevalence of non-communicable diseases, including DL, hyperglycemia (HG), and hypertension (HT) and their associated factors in an observational, single-center cohort of Vietnamese HIV-infected patients in the National Hospital for Tropical Disease in October and November 2016. In the second part of the study, we reviewed the incidence of CVD for all participants of a prospective cohort since its establishment to April 2017. The participants of the cohort visited the hospital every 6 months and follow-up period and the incidence rate were evaluated.

The study was approved by the Human Research Ethics Committee of the National Hospital for Tropical Disease and Hanoi City, Hanoi. All patients who were recruited in the study provided written informed consent for their clinical and laboratory data to be used and published for study purposes. The study was performed according to the principles expressed in the Declaration of Helsinki.

Measurements

Data collection of systolic and diastolic blood pressure (mmHg), casual blood sugar levels (mg/dL), and the lipid profile (triglycerides [TG], total cholesterol, and high-density lipoprotein [HDL] [mg/dL]) was performed in October and November 2016 for every patient who was registered in the cohort. Other data included the following: demographic variables (height, weight, sex, and age); a complete history of ART; a history of smoking; a history of CVD including stroke, congestive heart failure, and coronary artery disease; use of drugs for prophylaxis against opportunistic infections; CD4 cell counts (cells/mm3, measured by flow cytometry); and plasma HIV-RNA (copies/mL, measured using the Roche Cobas Taqman analyzer; Roche Molecular Diagnostics, Pleasanton, CA). Data were collected every 6 months until October 2017. Dyslipidemia was defined as TG levels > 150, HDL levels < 40, or c-LDL levels > 140 mg/dL (c-LDL was calculated as total cholesterol−HDL−TG/5). Hypertension was defined as systolic pressure > 140 mmHg or diastolic pressure > 90. HG was defined as casual blood glucose levels > 200 mg/dL. The incidence rate of CVD was calculated as the number of CVD cases divided by person-years observed in the cohort from the time of enrollment of the cohort to April 2017.

Statistical analysis

Statistical analysis was performed for descriptive data (mean and standard deviation), and univariate and multivariate analyses. Absolute and relative frequencies were used for continuous and categorical variables, respectively. To evaluate the association between exposure to LPV/r and other categorical variables, the chi-square or Fisher's exact test was applied as required. The independent t test or one-way ANOVA was used to compare means, and in case of asymmetry, the Mann-Whitney or Kruskal-Wallis test was also used.

Variables that were significantly associated with non-communicable diseases and CVD in univariate analysis were included in multivariate analysis. Logistic regression was used to determine the factors associated with non-communicable diseases in univariate and multivariate analyses. Cox proportional hazards regression was used to determine the factors associated with the incidence of CVD in univariate and multivariate analyses.

Statistical significance was defined as a two-sided p value < 0.05. We used odds ratios (ORs) and 95% confidence intervals (95% CIs) to estimate the association of each variable with non-communicable diseases. All statistical analyses were performed with SPSS ver. 25.0 (IBM SPSS, Chicago, IL).

Results

Table 1 shows the baseline characteristics of the subjects for the cross-sectional study. A total of 1,346 Vietnamese people with HIV were evaluated for the cross-sectional study. The subjects' mean age was 39.2 years and 41.8% of the patients were women. The mean body weight and body mass index were 56.2 kg and 21.4 kg/m^2, respectively, which represented a population with a low body weight. A total of 142 (10.5%) subjects were exposed to LPV/r. Subjects with LPV/r exposure had significantly higher serum creatinine, TG, and non-HDL cholesterol, and lower HDL levels compared with those without LPV/r exposure. However, there were no significant differences in basic demographics, including age, sex, and body weight, between subjects with and those without LPV/r exposure.

The prevalence of each non-communicable disease is shown in Table 2. The prevalence of DL, HT, and diabetes mellitus was 53.5%, 24.4%, and 24.4%, respectively. Of the subjects with DL, 669 (92.9%) subjects had hypertriglyceridemia. Tables 3, 4, and 5 show factors that were associated with DL, HT, and diabetes mellitus in univariate and multivariate analyses, respectively. Age (OR = 1.040; 95% CI, 1.025-1.055), female sex (OR = 0.335; 95% CI, 0.264-0.424), and LPV/r exposure (OR = 3.251; 95% CI, 2.030-5.207) were significantly associated with DL in multivariate analysis (Table 3). Older age was significantly associated with HG and HT in multivariate analysis (Tables 4 and 5). Exposure to LPV/r was significantly associated with HT in a protective manner in multivariate analysis (Table 5), which reflected lower diastolic blood pressure in subjects with LPV/r exposure.

Table 1. Baseline characteristics of Vietnamese patients with HIV on ART (n = 1,346)

Variables	LPV/r exposure-	LPV/r exposure+	Entire group	p value
Number of patients	1,204	142	1,346	
Age, years	39.2 ± 8.84	39.2 ± 8.57	39.2 ± 8.81	1.000
Female, *n* (%)	502 (41.7%)	61 (43.0%)	563 (41.8%)	0.773
Body weight, kg	56.3 ± 8.66	55.0 ± 8.83	56.2 ± 8.68	0.114
BMI, kg/m^2	21.4 ± 2.5	21.2 ± 2.8	21.4 ± 2.6	0.468
CD4+ count, /mL	483.1±197.9	475.7±212.4	482.3 ± 199.4	0.676
HIV RNA < 400 copies/mL	1180 (98.0%)	135 (95.1%)	1315 (97.8%)	0.032
Serum creatinine, mg/dL	0.85 ± 0.21	0.94 ± 0.23	0 .87 ± 0.22	< 0.001
Blood glucose, mg/dL	92.7 ± 20.6	94.4 ± 27.6	92.8 ± 21.5	0.384
Systolic blood pressure, mmHg	118.0 ± 15.5	117.6 ± 14.0	118.0 ± 15.3	0.739
Diastolic blood pressure, mmHg	75.5 ± 11.9	72.7 ± 10.5	75.2 ± 11.8	0.006
TG, mg/dL	192.2 ± 286.9	351.9 ± 553.5	209.0 ± 256.5	< 0.001
HDL, mg/dL	58.9 ± 23.1	51.5 ± 15.1	58.1 ± 22.5	< 0.001
non-HDL cholesterol, mg/dL	115.3 ± 46.6	138.8 ± 71.4	117.9 ± 50.3	< 0.001
Time from diagnosis of HIV infection, years	6.5 ± 3.8	10.3 ± 4.2	6.9 ± 4.1	< 0.001
Time from ART initiation, years	5.1 ± 3.0	8.6 ± 3.3	5.5 ± 3.2	< 0.001
Current smoking	283 (23.5%)	25 (17.6%)	308 (22.9%)	0.113

Data are expressed as mean ± SD or *n* (%). ART: antiretroviral therapy; HDL: high-density lipoprotein; LPV/r: ritonavir-boosted lopinavir; TG: triglycerides.

Table 2. Prevalence of non-communicable diseases in Vietnamese patients with HIV on ART (n = 1,346)

Non-communicable diseases	*n* (%)
Obesity	108 (8.0)
Hypertension (HT)	329 (24.4)
Hyperglycemia (HG)	11 (0.8)
Dyslipidemia (DL)	720 (53.5)
TG ≥ 150 mg/dL	669 (49.7)
HDL ≤ 39 mg/dL	209 (15.5)
Non-HDL cholesterol ≥ 210 mg/dL	47 (3.5)

Data are expressed as *n* (%). HDL: high-density lipoprotein; TG: triglycerides.

With regard to the incidence rate of CVD, 15 CVD events (incidence rate of CVD: 1.87/1,000 person-years) occurred in the cohort during the study period, with a mean follow-up period of 4.6 years and 8,013 person-years. Of the 15 CVD cases, two cases were coronary artery disease, 11 cases were stroke, and one case was congestive heart failure. In the Cox proportional hazard model, exposure to LPV/r was not significantly associated with the incidence of CVD (hazard ratio = 1.417; 95% CI, 0.446-4.498; p = 0.554). Age was the only factor that was associated with the incidence of CVD (hazard ratio = 1.123; 95% CI, 1.075-1.172; p < 0.001). Other non-communicable diseases, exposure of abacavir, and a history of smoking were not associated with the incidence of CVD.

Discussion

We evaluated the prevalence of non-communicable diseases and their associated factors among well-controlled Vietnamese people with HIV on ART. The prevalence of DL was 53.5%, which was disproportionally high compared with that of HG (0.8%) and HT (24.4%). LPV/r was strongly associated with DL in addition to known risk factors. However, exposure to LPV/r was not associated with the incidence of CVD. This could be partly attributable to underestimation of the incidence of CVD because a considerable number of the cause of deaths in this cohort remains unknown. Importantly, this is the first study that not only showed that exposure to LPV/r was strongly associated with DL, but it also estimated the incidence rate of CVD and its risk factors among Vietnamese people with HIV on ART.

Protease inhibitors affect the lipid profile and may cause CVD. Previous studies have suggested that using LPV/r can enhance renal toxicity of tenofovir and LPV/r is associated with renal dysfunction (*11,12*). Depending on the situation, substitution of other protease inhibitors, such as ritonavir-boosted darunavir or integrase inhibitors, for LPV/r can be used as salvage regimens (*13*). If this is not possible because of budget limitations, lipid-lowering therapy can be beneficial in people who are taking LPV/r with known risk factors, including older age, HT, and diabetes mellitus (*14-18*).

Our study has several limitations. In this prospective cohort, information on the cause of death or reason of loss to follow-up was partially missing. This could have led to underestimation of the incidence of CVD as mentioned above. Furthermore, some cases of CVD occurred before the timing of our cross-sectional study, which failed to reflect a causative relation between CVD and non-communicable diseases. In fact, non-communicable diseases, which are known as risk factors, were not significantly associated with the incidence of CVD in our study. Related to this limitation, information about treatment for non-communicable diseases, including lipid-lowering therapy, was not reflected in this analysis. This could have led to underestimation of

Table 3. Associated factors for dyslipidemia (DL) as estimated by univariate and multivariate analyses (n = 1,346)

Variables	Univariate analysis		Multivariate analysis		p value
	OR	95% CI	OR	95% CI	
Age per year-increase	1.053	1.039-1.068	1.040	1.025-1.055	< 0.001
Female	0.323	0.258-0.404	0.335	0.264-0.424	< 0.001
BMI per 1 kg/m^2-decrement	1.193	1.140-1.249			
CD4+ cell count per cell/μL	1.101	0.999-1.001			
HIV RNA > 400 copies/mL	0.755	0.365-1.559			
Time from diagnosis of HIV infection per year-increase	1.072	1.043-1.102	1.007	0.957-1.059	0.799
Time from initiation of ART per year-increase	1.123	1.085-1.163	1.065	0.998-1.138	0.059
Exposure of LPVr	3.347	2.222-5.042	3.251	2.030-5.207	< 0.001
Exposure of TDF	0.998	0.763-1.305			
Exposure of ABC	2.033	1.075-3.846	0.769	0.357-1.660	0.504

ABC: abacavir; ART: antiretroviral therapy; CI: confidence interval; LPV/r: ritonavir-boosted lopinavir; OR: odds ratio; TDF: tenofovir disoproxil fumarate.

Table 4. Associated factors for hyperglycemia (HG) as estimated by univariate and multivariate analyses (n = 1,346)

Variables	Univariate analysis		Multivariate analysis		p value
	OR	95% CI	OR	95% CI	
Age per year-increase	1.082	1.029-1.137	1.075	1.017 – 1.136	0.011
Female	0.519	0.137-1.965			
BMI per 1 kg/m^2-decrement	1.149	0.932-1.417			
CD4+ cell count per cell/μL	1.002	0.999-1.004			
HIV RNA > 400 copies/mL	0.000	0.000–			
Time from diagnosis of HIV infection per year-increase	1.160	1.018-1.321	0.829	0.541-1.271	0.390
Time from initiation of ART per year-increase	1.337	1.119-1.598	1.542	0.952-2.500	0.079
Exposure of LPVr	3.227	0.846-12.304			
Exposure of TDF	0.664	0.175-2.518			
Exposure of ABC	6.520	1.368-31.071	2.764	0.466-16.387	0.263

ABC: abacavir; ART: antiretroviral therapy; CI: confidence interval; LPV/r: ritonavir-boosted lopinavir; OR: odds ratio; TDF: tenofovir disoproxil fumarate.

Table 5. Associated factors for hypertension (HT) as estimated by univariate and multivariate analyses (n = 1,346)

Variables	Univariate analysis		Multivariate analysis		p value
	OR	95% CI	OR	95% CI	
Age per year-increase	1.061	1.046-1.076	1.051	1.035-1.067	< 0.001
Female	0.363	0.274-0.479	0.432	0.322-0.577	< 0.001
BMI per 1 kg/m^2-decrement	1.155	1.100-1.213	1.119	1.063-1.177	< 0.001
CD4+ cell count per cell/μL	0.999	0.999-1.000	1.000	0.999-1.000	0.535
HIV RNA > 400 copies/mL	0.939	0.399-2.208			
Time from diagnosis of HIV infection per year-increase	1.001	0.971-1.032			
Time from initiation of ART per year-increase	1.035	0.996-1.075			
Exposure of LPVr	0.633	0.403-0.993	0.623	0.390-0.996	0.048
Exposure of TDF	0.854	0.419-1.741			
Exposure of ABC	0.854	0.419-1.741			

ABC: abacavir; ART: antiretroviral therapy; CI: confidence interval; LPV/r: ritonavir-boosted lopinavir; OR: odds ratio; TDF: tenofovir disoproxil fumarate.

the prevalence of non-communicable diseases. Although this study did not identify LPV/r as a risk factor for the incidence of CVD, attention should be paid to preventing the incidence of CVD in people who are taking LPV/r with known risk factors.

In conclusion, the present study shows a high prevalence of DL in Vietnamese people with HIV and exposure to LPV/r is strongly associated with DL, in addition to other known risk factors. Attention to CVD is necessary for patients on LPV/r in consideration of their aging in the future.

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Conflicts of interest

S.O. has received research grants/materials from Japan Tobacco/Trii Pharmaceutical, MSD K.K., and CSL Behring, and has received honorariums from Torii Pharmaceutical, Co., MSD K.K., Gilead Sciences, and ViiV Healthcare. H.G. has received honorariums from MSD K.K., Abbott Japan, Co., Janssen Pharmaceutical K.K., Torii Pharmaceutical, Co., Roche Diagnostics K.K., and ViiV Healthcare, Co.

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