





ORIGINAL RESEARCH

HIV Infection and Long-Term Residual Cardiovascular Risk After Acute Coronary Syndrome

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BACKGROUND: It is unclear whether HIV infection affects the long-term prognosis after an acute coronary syndrome (ACS). The objective of the current study was to compare rates of major adverse cardiac and cerebrovascular events after a first ACS between people living with HIV (PLHIV) and HIV-uninfected (HIV-) patients, and to identify determinants of cardiovascular prognosis.

METHODS AND RESULTS: Consecutive PLHIV and matched HIV- patients with a first episode of ACS were enrolled in 23 coronary intensive care units in France. Patients were matched for age, sex, and ACS type. The primary end point was major adverse cardiac and cerebrovascular events (cardiac death, recurrent ACS, recurrent coronary revascularization, and stroke) at 36-month follow-up. A total of 103 PLHIV and 195 HIV- patients (mean age, 49 years [SD, 9 years]; 94.0% men) were included. After a mean of 36.6 months (SD, 6.1 months) of follow-up, the risk of major adverse cardiac and cerebrovascular events was not statistically significant between PLHIV and HIV- patients (17.8% and 15.1%, $P=0.22$; multivariable hazard ratio [HR], 1.60; 95% CI, 0.67–3.82 [$P=0.29$]). Recurrence of ACS was more frequent among PLHIV (multivariable HR, 6.31; 95% CI, 1.32–30.21 [$P=0.02$]). Stratified multivariable Cox models showed that HIV infection was the only independent predictor for ACS recurrence. PLHIV were less likely to stop smoking (47% versus 75%; $P=0.01$) and had smaller total cholesterol decreases (-22.3 versus -35.0 mg/dL; $P=0.04$).

CONCLUSIONS: Although the overall risk of major adverse cardiac and cerebrovascular events was not statistically significant between PLHIV and HIV- individuals, PLHIV had a higher rate of recurrent ACS.

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Key Words: acute coronary syndrome ■ coronary artery disease ■ dyslipidemia ■ heart disease ■ HIV

See Editorial by Erqou and Rodriguez-Barradas

The risk of coronary heart disease is significantly increased among people living with HIV (PLHIV) who are taking antiretroviral therapy.^{1,2} The

potential mechanisms are complex and multifactorial, including the role of HIV infection itself (direct or indirect, via immune activation); the impact of metabolic

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CLINICAL PERSPECTIVE

What Is New?

- We observed a higher risk of recurrent ischemic events and hospitalizations for heart failure after a first acute coronary syndrome in patients infected with HIV compared with matched non-HIV-infected patients in this prospective study with long follow-up.
- Post-acute coronary syndrome, patients infected with HIV exhibit a worse cardiovascular risk profile with less attainment of lipid goals and more persistent active smoking compared with their non-HIV counterparts.

What Are the Clinical Implications?

- Our findings suggest that optimizing primary and secondary cardiovascular prevention strategies in the HIV-infected population is warranted; in particular, smoking cessation and intensification of lipid-lowering therapies after acute coronary syndrome should be priorities.
- Our clinical study encourages epidemiological and pathophysiological studies on coronary artery disease in patients infected with HIV to better understand the higher risk of myocardial infarction and recurrent ischemic events.
- New findings on higher platelet reactivity could provide new insights into the higher risk of atherothrombosis in people living with HIV and could lead to specific new therapies.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
HF	heart failure
HR	hazard ratio
MACCE	major adverse cardiac and cerebrovascular events
MI	myocardial infarction
OR	odds ratio
PACS-HIV	Prognosis of Acute Coronary Syndrome in HIV-Infected Patients
PCI	percutaneous coronary intervention
PLHIV	people living with HIV
STEMI	ST-segment-elevation myocardial infarction

disturbances secondary to some antiretroviral drugs, particularly protease inhibitors (lipid and glucose abnormalities); the overrepresentation of traditional risk factors (eg, smoking); more frequent illicit drug use (eg, cocaine); and genetic background.²⁻⁴ PLHIV also tend

to develop coronary heart disease at a younger age than HIV-uninfected (HIV-) individuals, possibly attributable to the lower median age of this population, but potentially also because of an earlier and higher exposure to cardiovascular risk factors and comorbidities.^{2,5}

Whether HIV infection is an independent risk factor for recurrent ischemic events and clinical restenosis after a first episode of an acute coronary syndrome (ACS) has been poorly studied and results are conflicting.^{6,7} During the acute phase of ACS, studies including an HIV- control group did not find any significant difference in cardiovascular mortality.⁸⁻¹³ However, after 1-year follow-up, some studies have shown that PLHIV have a higher rate of recurrent ischemic events compared with HIV- controls, but without differences in total and coronary heart disease mortality,^{8,9,14} whereas other studies did not.^{10,15} The rate of clinical restenosis after percutaneous coronary intervention (PCI) is also variable after 1-year follow-up, ranging from 9% to 52% among PLHIV.^{8,9,16,17} Studies that included an HIV- control group did not find any significant difference in coronary restenosis when stenting was performed.^{9,16-18} Currently, coronary restenosis using new-generation drug-eluting stents does not seem to cause clinical concern.^{19,20}

The aims of the present study were to compare the rate of cardiovascular events after a first ACS between PLHIV and HIV- individuals during long-term follow-up, and to identify the determinants of cardiovascular prognosis.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Patient Population

The study design and primary results for the 1-year follow-up have been previously reported.⁹ Briefly, we prospectively included consecutive PLHIV with a first episode of ACS in 23 different coronary intensive care units in France between September 2003 and March 2006. The last patient was followed up until April 2009. Two HIV- patients were enrolled and matched for age (± 5 years), sex, and type of ACS (ST-segment-elevation myocardial infarction [STEMI], non-ST-segment-elevation myocardial infarction [NSTEMI], or unstable angina) in the same center a maximum of 6 months after enrollment of each PLHIV. Patient characteristics, cardiovascular risk factors and therapies, medical histories, and baseline clinical data were collected prospectively (clinical visits with a cardiologist at months 1, 6, 12, 18, 24, and 36 after the first episode of ACS). Participants were followed longitudinally for incident cardiovascular disease events and

cause-specific mortality during a prespecified follow-up time of 36 months.

Study End Points

The primary and secondary end points have already been described in the 1-year follow-up report.⁹ At each prespecified visit, cardiovascular risk factors, therapies, incident cardiovascular, and other noncardiovascular events were recorded. An independent clinical events committee unaware of the patients' HIV status adjudicated all clinical end points.

The primary end point was a composite of major adverse cardiac and cerebrovascular events (MACCE) comprising cardiac death, recurrent ACS (STEMI, NSTEMI, or unstable angina requiring hospitalization), recurrent coronary revascularization (PCI or coronary artery bypass graft, urgent or nonurgent), and stroke. For patients who developed >1 cardiovascular event during follow-up, we counted the first cardiovascular event and censored subsequent events at the time of occurrence of the first event for the primary end point. Cardiac death included any death with a cardiac cause (eg, myocardial infarction [MI], congestive heart failure [HF], low-output failure, and fatal arrhythmia), unwitnessed death, and sudden cardiac death. We also report cumulative events after the first cardiovascular event.

Other cardiovascular primary end points were: (1) target lesion revascularization, defined as any repeat PCI or bypass surgery of the initial culprit lesion for recurrent angina, or ischemia; (2) target vessel revascularization, defined as any clinically driven repeat PCI or bypass surgery of the entire target vessel; and (3) target vessel failure, defined as a composite end point of cardiac death, MI, and clinically driven target lesion revascularization. Therefore, we could ascertain whether the recurrent ischemic event was related to the initial culprit lesion (target lesion revascularization) or to a new coronary lesion on another segment or artery. Myocardial infarction (MI) was defined as the presence of at least 2 of the following: ischemic symptoms, elevation in cardiac enzymes (troponin I or T) at least twice their upper normal limits, and new ECG changes compatible with MI.²¹ Secondary end points included an episode of HF requiring hospitalization, stable angina, silent myocardial ischemia (defined as the presence of objective evidence of myocardial ischemia during ischemic tests [treadmill testing, stress echocardiography, and/or single-photon emission computed tomography] in the absence of chest discomfort reported by the cardiologist at each visit), supraventricular or ventricular arrhythmias (reported by the cardiologist at each visit), peripheral vascular disease (including any endovascular surgery or dilatation for carotid or limb diseases), and venous thromboembolic disease requiring hospitalization.

Smoking status and newly diagnosed hypertension and diabetes mellitus were systematically evaluated during the entire follow-up. Fasting lipid parameters including low- and high-density lipoprotein cholesterol, total cholesterol, and triglycerides were proposed to be evaluated at each local laboratory during each prespecified visit. Information on the use of stress testing (including exercise ECG, single-photon emission computed tomography, and dobutamine stress echocardiography) and echocardiography including left ventricular ejection fraction measurement were collected during the entire follow-up.

Statistical Analysis

Using a 2-sided test, with a type 1 error of 5%, the study had an 80% power to detect a hazard ratio (HR) of 1.8 for MACCE over the 3-year follow-up, assuming a 25% rate in HIV- patients by including 100 PLHIV and 200 HIV- patients. Kaplan-Meier estimates were calculated and plotted for rates of MACCE cardiovascular death, recurrent ACS, recurrent coronary revascularization, and stroke events in each group 36 months after entry into the study. HRs for the occurrence of events were estimated using a stratified univariable Cox model, which took the matching into account. Time to event was defined as the time between entry into the coronary care unit and occurrence of the event, dropout, or 36 months after entry into the study, whichever occurred first. Patients who died from noncardiovascular cause were censored at the time of their death.

Stratified univariable and multivariable Cox models were performed to determine factors associated with a higher risk of MACCE and with a higher risk of recurrent ACS at 36 months. Factors differentiating the 2 groups at baseline with $P < 0.05$ were analyzed in the univariable models: illicit drug use, body mass index (\geq versus < 25 kg/m²), low-density lipoprotein cholesterol ($>$ versus ≤ 100 mg/dL), triglycerides ($>$ versus ≤ 150 mg/dL), and white blood cell count. All of these factors were included in the multivariable model.

All values missing for <50% of individuals were replaced by using a multiple imputation method, and missing values were randomly sampled from their predicted distributions. Predicted distributions were calculated for an arbitrary missing data pattern using Markov chain Monte Carlo method. Ten sets of imputations were used to create 10 complete data sets. All 10 data sets were analyzed and combined with Rubin's rules.²²

The study complied with the Declaration of Helsinki and was approved by the Committee for the Protection of Human Subjects in Biomedical Research of Saint-Antoine University Hospital, Paris, France. Written informed consent to participate in the study was obtained

from all patients. There was no patient involvement in the design or analysis of this study. However, patient representatives have been involved in the review of the letter of information and consent form.

RESULTS

Study Population

The flow chart of the PACS-HIV (Prognosis of Acute Coronary Syndrome in HIV-Infected Patients) study is depicted in Figure S1. Baseline characteristics of the cohort have already been published.⁹ Briefly, a total of 103 PLHIV (mean age, 49 years [SD, 9 years]; 94.0% men) and 195 HIV- patients (mean age, 50 years [SD, 10 years]; 94.4% men) hospitalized with a first episode of ACS were included. PLHIV had a long history of know HIV disease (mean, 12 years [SD, 8 years]) with median nadir and baseline CD4 cell counts of 123 (quartile 1=52, quartile 2=210) and 462 (quartile 1=270, quartile 2=640) per μL , respectively. After a mean of 36.6 months (SD, 6.1 months) of follow-up, 7 patients were lost to follow-up and 14 patients had died (6 from cardiovascular causes and 8 from other causes) (Figure S1).

Primary End Points

Table 1 shows the distribution of all cardiovascular events during the 36-month follow-up. The probability of MACCE at 36 months was 17.8% in the PLHIV group and 15.1% in HIV- patients (Figure 1A), with no statistically significant difference between the 2 groups (univariable HR, 1.48; 95% CI, 0.79–2.76 [$P=0.22$]; multivariable HR, 1.60; 95% CI, 0.67–3.82 [$P=0.29$] (Table 2). There were also no significant differences in cardiovascular death (univariable HR, 2.00; 95% CI, 0.40–9.91 [$P=0.40$]) (Figure 1B), recurrent coronary revascularization (univariable HR, 1.08; 95% CI, 0.53–2.22 [$P=0.83$]) (Figure 1C), or stroke (Figure 1D), but PLHIV experienced a higher risk of recurrent ACS than HIV- patients (univariable HR, 3.44; 95% CI, 1.34–8.79 [$P=0.01$]) (Figure 1E). After accounting for confounding factors, the risk of recurrent ACS was 6-fold higher among PLHIV (multivariable HR, 6.31; 95% CI, 1.32–30.21 [$P=0.02$]) (Table 2).

When we restricted the recurrence of ACS to patients without recurrent ACS at month 12, we did not observe any difference between PLHIV and HIV- patients (HR, 0.83; 95% CI, 0.15–4.66 [$P=0.83$]) (Figure S2A), whereas the risk of recurrent ACS during the first 12 months was higher in the PLHIV group (HR, 7.14; 95% CI, 1.96–26.00 [$P=0.003$]) (Figure S2B).

The rates of target lesion revascularization, target vessel revascularization, and target vessel failure were not significantly different between the PLHIV group and HIV- patients (Figure 2). Thirty-six patients (12 PLHIV and 24 HIV- patients; Table 1) had repeated coronary revascularization during the entire follow-up. Fifteen patients (8

Table 1. Number of MACCE During 36 Months of Follow-Up

	PLHIV (n=103)	HIV- (n=195)
Primary end point, events (individuals affected)		
No. of MACCE	22 (18)*	39 (29) [†]
Cardiovascular death	3 (3)	3 (3)
Recurrent ACS	14 (12)	15 (11)
NSTEMI	2 (2)	6 (3)
STEMI	2 (2)	1 (1)
Unstable angina	10 (8)	8 (7)
Recurrent coronary revascularization	15 (12)	27 (24)
Urgent	11 (8)	9 (7)
Nonurgent	4 (4)	18 (17)
Stroke	0	3 (3)
Other primary end points, events (individuals affected)		
Target lesion revascularization	9 (7)	18 (17)
Target vessel revascularization	12 (10)	22 (20)
Target vessel failure	17 (13)	30 (24)
Secondary end points, events (individuals affected)		
HF requiring hospitalization	12 (6)	3 (3)
Stable angina	6 (4)	13 (13)
Silent myocardial ischemia	7 (6)	20 (16)
Supraventricular arrhythmias	3 (3)	2 (2)
Peripheral vascular disease	7 (4)	2 (2)
Venous thromboembolic disease	2 (2)	1 (1)

HF indicates heart failure; NSTEMI, non-ST-segment-elevation myocardial infarction; PLHIV, people living with HIV; and STEMI, ST-segment-elevation myocardial infarction.

*Twenty-two major adverse cardiac and cerebrovascular events (MACCE) in 18 individuals; 10 acute coronary syndromes (ACS) and recurrent coronary revascularization occurred at the same time.

[†]Thirty-nine MACCE events in 29 individuals; 9 ACS and recurrent coronary revascularization occurred at the same time.

PLHIV and 7 HIV-) had urgent coronary revascularization with PCI (HR, 2.58; 95% CI, 0.89–7.52 [$P=0.08$]) and 21 (4 PLHIV and 17 HIV-) had nonurgent revascularization (HR, 0.50; 95% CI, 0.16–1.51 [$P=0.22$]) (Table 1, Figure S3).

Among PLHIV, recurrent PCI was predominantly driven by ACS (67%), followed by stable angina (17%) and silent myocardial ischemia (17%); in HIV- patients, it was more evenly distributed: silent myocardial ischemia (38%), stable angina (33%), and ACS (29%). Nine patients had a second MACCE (cumulative incidence, 19.5%; 95% CI, 10.2%–35.3% by 36-month follow-up) with a median time to occurrence of 113 (quartile 1=19, quartile 3=379) days. Most recurrent ischemic events were related to a new lesion on another coronary segment or artery (>65% of cases, similarly in both group).

Secondary End Points

Table 1 also depicts the secondary cardiovascular events during the entire follow-up. Only HF requiring

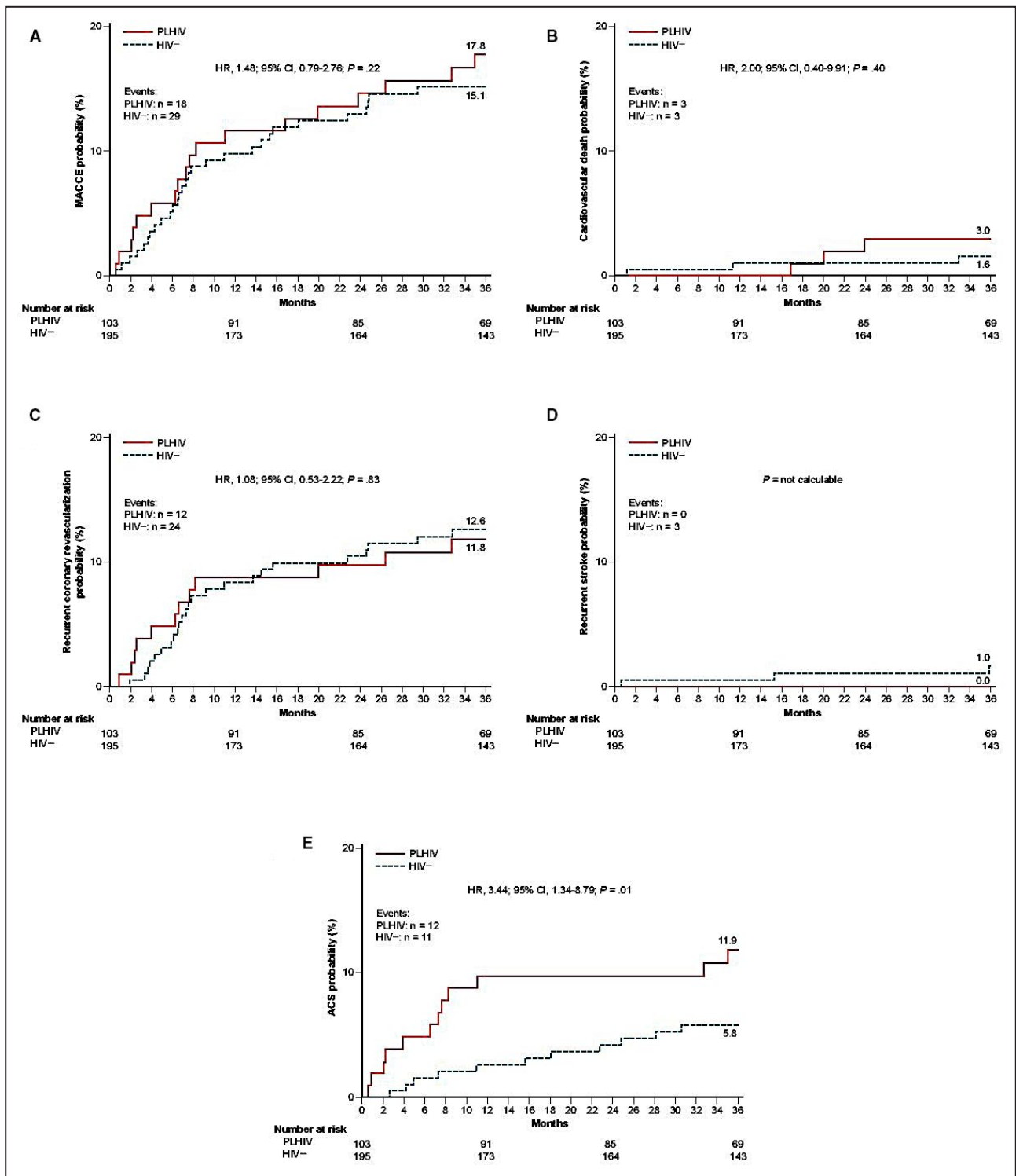


Figure 1. Kaplan-Meier plots by HIV status.

A, Major adverse cardiac and cerebrovascular events (MACCE). **B**, Cardiovascular death. **C**, Recurrent coronary revascularization. **D**, Stroke. **E**, Recurrent acute coronary syndrome (ACS). HR indicates hazard ratio; and PLHIV, people living with HIV.

hospitalization was significantly more frequent in the PLHIV group versus HIV- patients (HR, 6.24; 95% CI, 1.24–31.34 [$P=0.03$]) (Figure S4). Silent myocardial ischemia was more frequent among HIV- patients (16

HIV- versus 6 PLHIV) as a result of higher use of ischemia testing in the HIV- group (mean number of ischemia tests during follow-up: 2.0 [SD, 1.3] versus 1.7 [SD, 1.2]; $P=0.03$).

Table 2. Stratified Univariable and Multivariable Cox Models, Separately for MACCE and ACS Risk

Group	MACCE (n=47)						ACS (n=23)					
	No. With Event(s)	Univariable		Multivariable		No. With Event(s)	Univariable		Multivariable			
		HR (95% CI)	P Value	HR (95% CI)	P Value		HR (95% CI)	P Value	HR (95% CI)	P Value		
HIV- (n=195)	29	1	0.22	1	0.29	11	1	0.01		0.02		
PLHIV (n=103)	18	1.48 (0.79–2.76)		1.60 (0.67–3.82)		12	3.44 (1.34–8.79)		6.31 (1.32–30.21)			
Illicit drug use			0.96		0.75			0.78		0.69		
No (n=262)	41	1		1		19	1		1			
Yes (n=36)	6	0.97 (0.33–2.86)		0.81 (0.21–3.14)		4	0.82 (0.20–3.30)		0.67 (0.10–4.63)			
BMI			0.31		0.24			0.54		0.48		
<25 kg/m ² (n=163)	32	1		1		16	1		1			
≥25 kg/m ² (n=135)	15	0.64 (0.26–1.53)		0.54 (0.19–1.51)		7	0.66 (0.18–2.47)		0.56 (0.11–2.80)			
LDL-C			0.04		0.05			0.26		0.23		
≤100 mg/dL (n=70)	7	1		1		3	1		1			
>100 mg/dL (n=228)	40	3.24 (1.05–10.01)		3.26 (0.99–10.75)		20	2.39 (0.53–10.74)		3.22 (0.48–21.76)			
Triglycerides			0.50		0.39			0.14		0.12		
≤150 mg/dL (n=149)	23	1		1		9	1		1			
>150 mg/dL (n=149)	24	1.30 (0.61–2.79)		1.47 (0.60–3.60)		14	2.31 (0.77–6.95)		2.69 (0.78–9.28)			
White blood cell count (continuous)	47	1.10 (0.99–1.22)	0.07	1.10 (0.98–1.24)	0.11	23	1.11 (0.95–1.29)	0.19	1.16 (0.95–1.41)	0.14		

ACS indicates acute coronary syndromes; BMI, body mass index; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACCE, major adverse cardiac and cerebrovascular event; and PLHIV, people living with HIV.

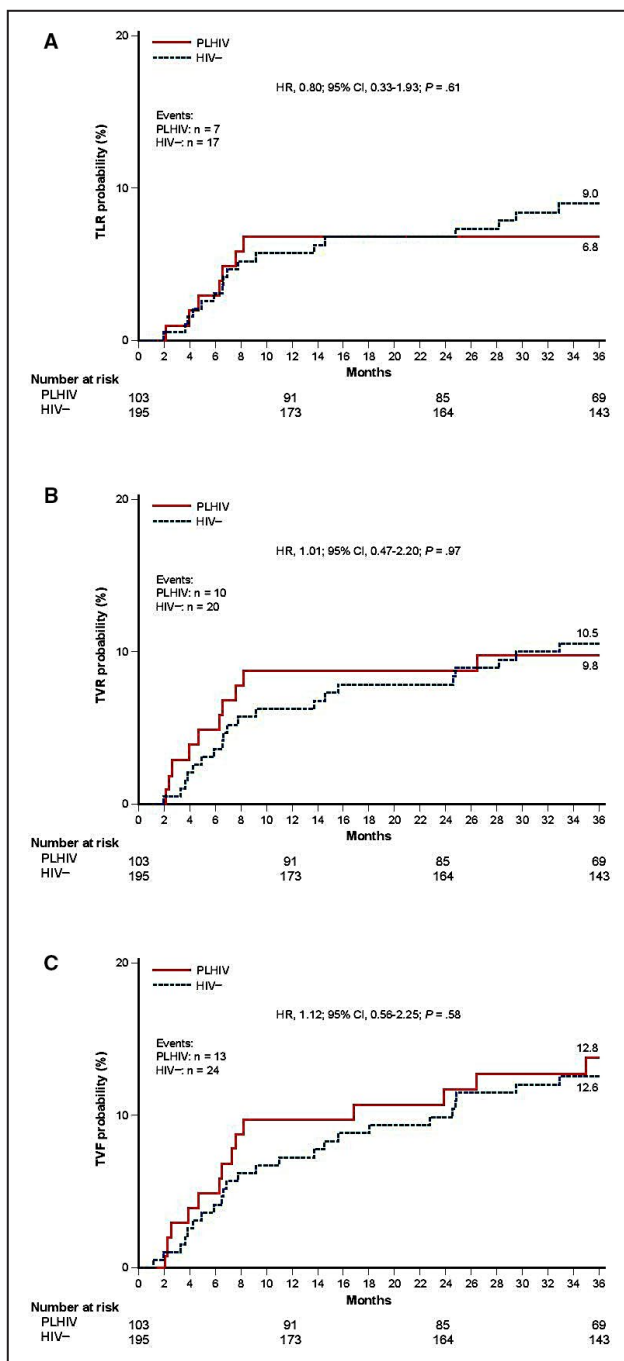


Figure 2. Kaplan-Meier plots by HIV status.

A, Target lesion revascularization (TLR). **B**, Target vessel revascularization (TVR). **C**, Target vessel failure (TVF). HR indicates hazard ratio; and PLHIV, people living with HIV.

Predictors of MACCE and Recurrent ACS

A multivariable Cox model for the risk of MACCE did not show any independent predictors in the entire cohort (Table 2). However, a multivariable Cox model for the risk of recurrent ACS showed that HIV infection was the only independent predictor of recurrent ACS (Table 2). We could not find any statistically significant

associations between any HIV parameters (eg, nadir and baseline CD4 cell count, HIV viral load, CD4/CD8 ratio, protease inhibitor use at index hospitalization, and time since HIV diagnosis) and an increased risk of recurrent ACS in the PLHIV group (data not shown).

Long-Term Residual Cardiovascular Risk

Table 3 depicts the variations in cardiometabolic parameters during the entire follow-up between PLHIV and HIV- patients. Patients were predominantly taking statins at initial discharge and follow-up, without a difference between the PLHIV and HIV- groups (96.1% versus 99.0% [$P=0.12$] and 86.2% versus 93.4% [$P=0.06$]). More PLHIV experienced a change of statin therapy (51.5% versus 38.5%; $P=0.03$). All patients received aspirin during follow-up. β -Blockers were prescribed at a similar rate in PLHIV and HIV- patients at discharge (56.3% versus 61.0%; $P=0.66$) and at 36 months (56.4% versus 66.1%; $P=0.22$).

In the PLHIV group, 47% stopped smoking and 3 nonsmokers at the onset of ACS started to smoke, whereas in the HIV- group, 75% stopped smoking and 4 nonsmokers at the onset of ACS started to smoke ($P=0.01$). Nonsignificantly different proportions of PLHIV and HIV- patients developed diabetes mellitus (11.5% versus 6.8%; $P=0.24$) and hypertension (5.2% versus 2.9%; $P=0.43$).

DISCUSSION

In the present multicenter, prospective, longitudinal study, after 3 years of follow-up, PLHIV had a favorable prognosis, with a rate of MACCE occurrence that was not statistically different from that of HIV- patients. However, PLHIV had a significantly higher rate of recurrent ACS at 3-year follow-up. This excess of recurrent ischemic events was predominantly driven by increased recurrent episodes of unstable angina, which led to a numerically increased rate of repeat urgent PCI compared with HIV- patients. These recurrent ischemic events were predominantly related to new coronary artery lesions.

Conflicting results exist regarding the long-term prognosis after ACS in PLHIV.^{6,8,10,14,15} A meta-analysis published in 2012 that included 2442 patients (from studies with and without a control HIV- group; median follow-up 25.5 months) concluded that PLHIV admitted for ACS had a substantial short-term in-hospital risk of death (8%) and a significant long-term risk of coronary revascularization (20%) and MI (9%), especially if they received protease inhibitors.⁶ Another meta-analysis, published in 2017, included 2268 patients (from 6 studies that compared PLHIV and HIV- patients).⁷ It did not find any difference in mortality or recurrent ischemic events after an ACS

Table 3. Comparison of Cardiometabolic Risk Factors Between PLHIV and HIV– Patients (Baseline, Last Follow-Up, and Difference from Baseline to Follow-Up)

	PLHIV (n=94)		HIV– (n=183)		P Value*
	No.	Mean (SD)	No.	Mean (SD)	
Baseline GRACE risk score	87	81.2 (18.2)	177	84.8 (18.7)	0.29
Baseline WBC count, / μ L	94	8200 (3000)	182	11 000 (4200)	<0.0001
Follow-up BMI, kg/m ²	90	22.9 (3.7)	181	27.8 (4.6)	
BMI difference, kg/m ²	90	0.5 (2.2)	181	0.6 (2.4)	0.71
Baseline total cholesterol, mg/dL	86	203.5 (50.3)	154	203.7 (50.7)	0.39
Follow-up total cholesterol, mg/dL	86	181.2 (47.2)	154	168.8 (42.1)	
Total cholesterol difference, mg/dL	86	–22.3 (54.7)	154	–35.0 (52.3)	0.04
Baseline LDL-C, mg/dL	72	123.2 (47.2)	148	133.0 (45.8)	0.04
Follow-up LDL-C, mg/dL	72	95.1 (38.4)	148	95.7 (32.3)	
LDL-C difference, mg/dL	72	–28.1 (48.1)	148	–37.3 (46.5)	0.21
Baseline HDL-C, mg/dL	75	39.6 (14.7)	151	42.6 (13.2)	0.10
Follow-up HDL-C, mg/dL	75	43.4 (18.4)	151	44.9 (11.6)	
HDL-C difference, mg/dL	75	3.7 (17.7)	151	2.3 (13.9)	0.26
Baseline TC:HDL-C	75	5.7 (2.4)	149	5.2 (1.9)	0.15
Follow-up TC:HDL-C	75	4.8 (2.4)	149	4.0 (1.4)	
TC:HDL-C difference	75	–0.9 (2.5)	149	–1.2 (2.0)	0.54
Baseline non-HDL-C, mg/dL	75	161.5 (47.1)	149	162.2 (49.2)	0.65
Follow-up non-HDL-C, mg/dL	75	137.4 (48.5)	149	123.4 (41.4)	
Non-HDL-C difference, mg/dL	75	–24.1 (52.0)	149	–38.8 (49.8)	0.09
Baseline triglycerides, mg/dL	85	246.6 (192.9)	154	172.5 (146.8)	0.008
Follow-up triglycerides, mg/dL	85	225.7 (170.6)	154	169.7 (214.9)	
Triglycerides difference, mg/dL	85	–20.9 (192.7)	154	–2.8 (231.0)	0.44
Baseline fasting glucose, mg/dL	81	106.4 (41.2)	112	118.8 (63.6)	0.58
Follow-up fasting glucose, mg/dL	81	103.1 (48.2)	112	107.0 (26.9)	
Fasting glucose difference, mg/dL	81	–3.3 (61.8)	112	–11.9 (63.3)	0.55
Baseline LVEF, %	83	55.4 (11.3)	164	54.8 (9.3)	0.77
Follow-up LVEF, %	83	56.5 (11.8)	164	55.3 (8.6)	
LVEF difference, %	83	1.1 (4.5)	164	0.4 (3.5)	0.36

BMI indicates body mass index; GRACE, Global Registry of Acute Coronary Events; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; TC, total cholesterol; and WBC, white blood cell.

*P value by conditional logistic regression.

between PLHIV and HIV– patients during follow-up times between 1 and 3.1 years (odds ratio [OR], 1.13; 95% CI, 0.65–1.96 [$P=0.66$ for total mortality]; OR, 1.16; 95% CI, 0.50–2.68 [$P=0.74$ for cardiac death]).⁷ Recently, a multicenter US cohort study observed that mortality after MI was higher after initial type 2 MI compared with initial type 1 MI (22.2 versus 8.2 per 100 person-years after 5-year follow-up).²⁰

Two studies have reported that PLHIV have a higher rate of recurrent ACS (including STEMI, NSTEMI, and unstable angina) compared with HIV– controls, but showed that long-term cardiovascular and overall mortality did not differ.^{8,9} One study found that PLHIV had a higher risk of death during the first year after an ACS.¹⁴ However, 2 other studies^{10,15} found that the long-term prognosis after ACS was similar for PLHIV and HIV– patients, without an increased risk of recurrent ACS.

Possible rationale to explain these discrepancies is discussed below.

First, there were differences in study design (eg, prospective data collection and retrospective database collection) and definitions of ACS (eg, only STEMI and NSTEMI^{8,10,14,15} or unstable angina).^{9,17,18} Some studies included patients with ACS who had a first MI,^{14,15} while others included patients who had a previous MI or this information was not detailed.^{8,10,17,18}

Second, the HIV characteristics of the included PLHIV might have been different in the various studies, particularly in terms of immunosuppression, with various rates of patients with viral suppression and nadir levels of CD4 that might impact the overall prognosis.^{4,23} In fact, the impact of low nadir CD4 cell count (<200/ μ L) on coronary atherosclerosis, peripheral vascular disease, and events has been

documented.^{24–26} Recently, Peyracchia et al²⁷ found that PLHIV with CD4 cells <200 per μL were more likely to have coronary hypoechoic plaques, major acute cardiovascular events, and MI recurrence than those with higher CD4 cell counts after ACS. Our study suggests that HIV infection itself has a role, as it was an independent predictor of recurrent ACS. This highlights the plausible specific and complex direct role of the HIV virus itself and its indirect effects (via immune activation) on the atherothrombotic process in this population. However, we could not find any HIV-specific parameters associated with this increased ischemic risk. Furthermore, we observed in the present study that recurrent ACS was related to new coronary artery lesions (similarly in both groups), suggesting an accelerated coronary atherosclerosis process. This is in line with a recent report on the long-term prognosis of ACS in a large French cohort of patients <45 years.¹⁹ This study found that ethnicity, inflammatory disease including chronic HIV infection, and persistent smoking were the strongest correlates of a first recurrent event (predominantly MI) and related to new coronary lesion in two thirds of patients,¹⁹ which is in line with our results.

Interestingly, we observed that the cardiovascular residual risk profile after ACS was worse among PLHIV, who had a smaller decrease in total cholesterol and a lower rate of smoking cessation compared with the HIV– group.

Study Limitations

Although the PACS-HIV study is the largest longitudinal, multicenter, prospective study with the longest prespecified, prospective, long-term follow-up reported, this observational study did not evaluate adherence to any therapies and could have led to bias in interpreting the increased rate of ACS, HF, and worse atherogenic lipid profile observed in the PLHIV group. However, drug prescriptions were reported in the case report form at each prespecified visit and no differences were observed between PLHIV and HIV– patients for any cardiovascular drugs, apart from the lower rate of high-intensity statins in the PLHIV group.

CONCLUSIONS

The results of our prospective study comparing PLHIV and matched HIV– patients with a first episode of ACS showed that the rate of MACCE was not statistically different in the 2 groups after long-term follow-up. However, PLHIV exhibited a higher rate of recurrent ACS, predominantly related to new coronary lesions, particularly during the first year, and had an increased rate of HF requiring hospitalization. PLHIV also had a worse cardiovascular residual risk profile, with lower

smoking cessation rates and smaller total cholesterol decreases, highlighting the need for enhanced secondary prevention.

APPENDIX

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Disclosures

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Supplementary Materials

Figures S1–S4

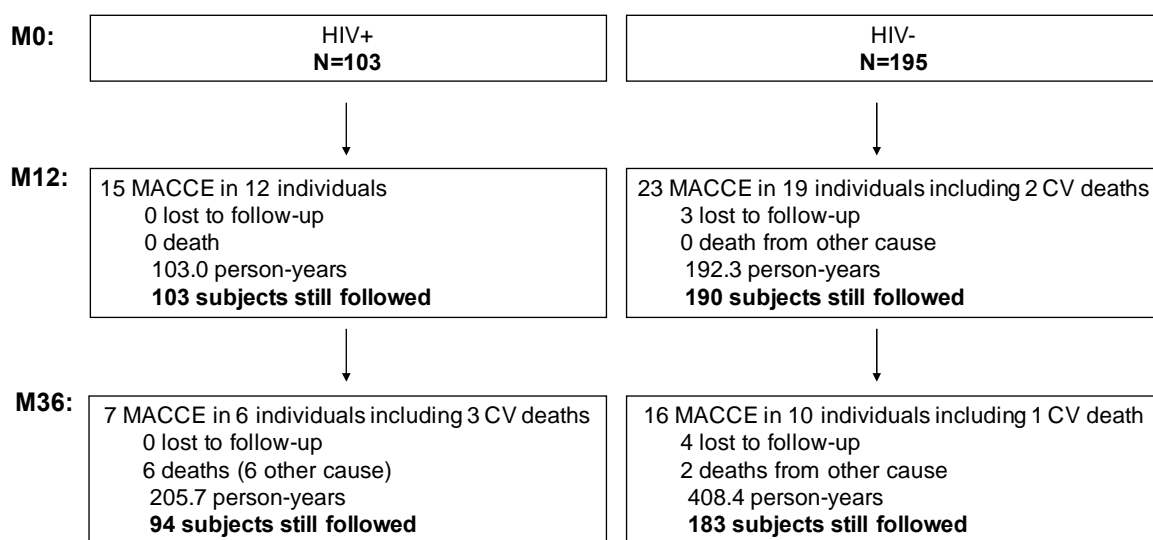
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SUPPLEMENTAL MATERIAL

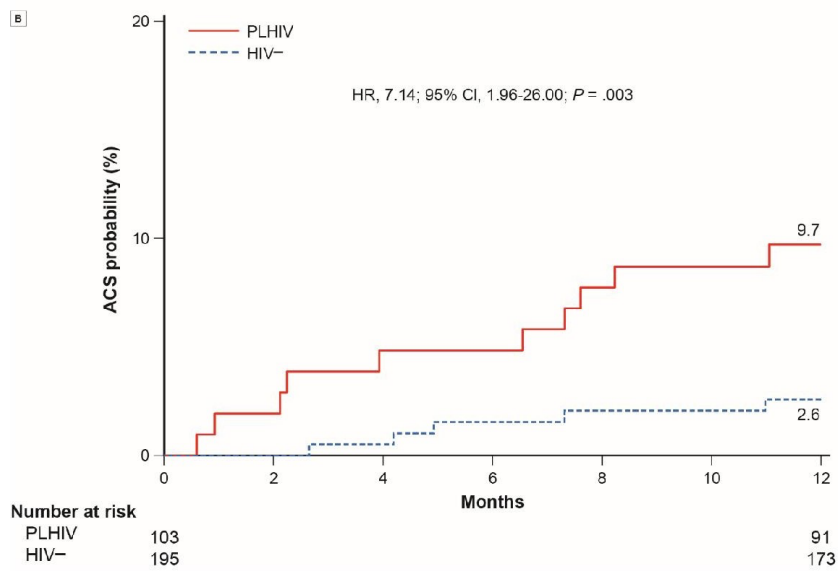
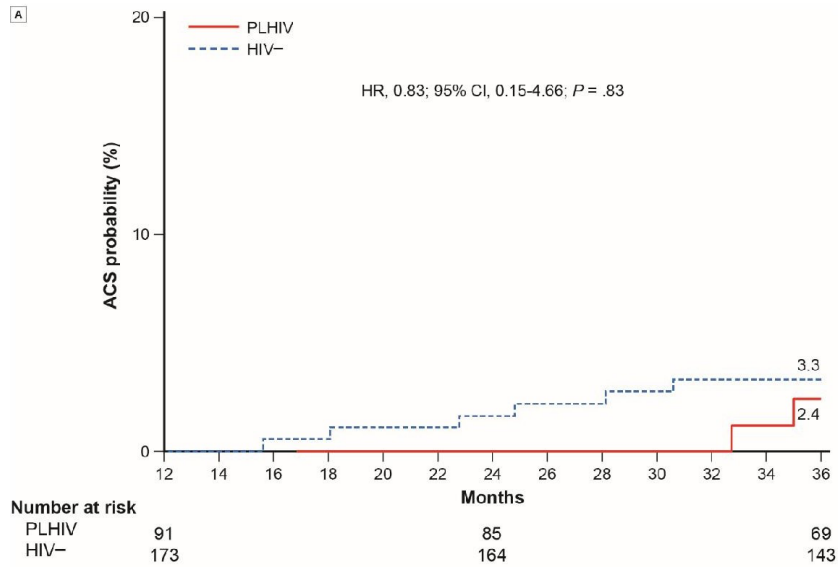
Figure S1. Flow chart of the PACS-HIV study.



Compared with our first publication for the 12-month follow up⁹, in the present study, we have added three more patients who had MACCE event(s) that occurred during the 12-month follow-up but that were detected after the database was locked (two HIV+ patients and one HIV— patient).

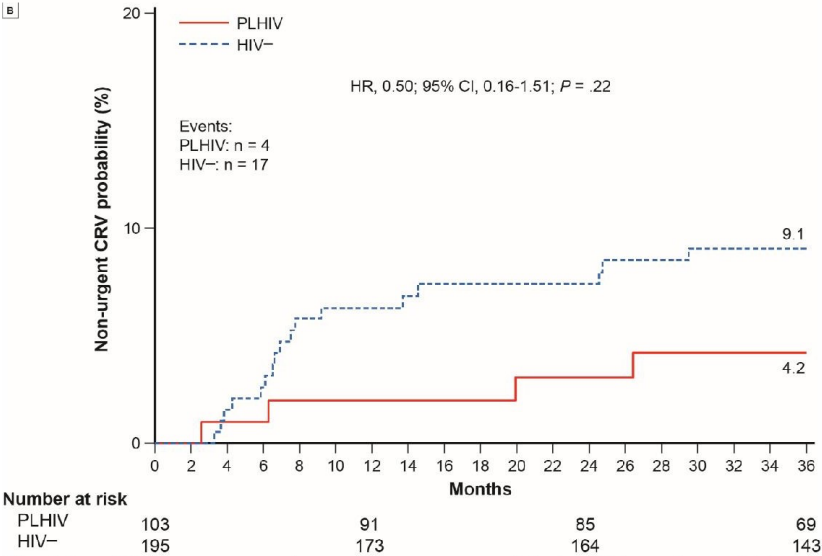
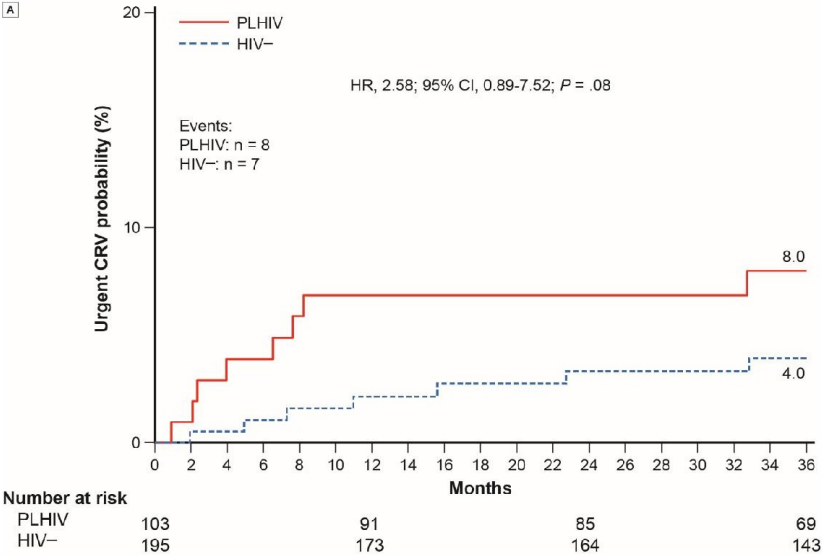
CV, cardiovascular; MACCE, major adverse cardiac and cerebrovascular events; MO, baseline visit; M12, visit at month 12; M36, visit at month 36; PLHIV, people living with human immunodeficiency virus.

Figure S2. Kaplan-Meier Plots by HIV Status for ACS.



A, At 36 months in Individuals Without ACS at Month 12. B, At 12 months.

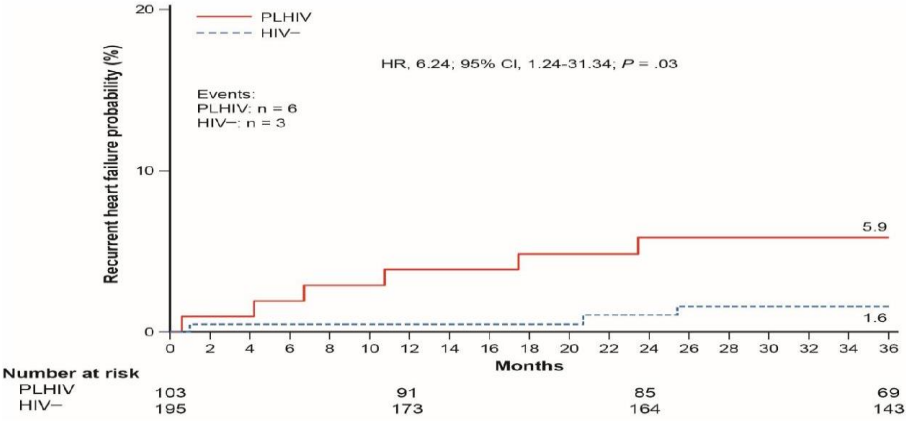
Figure S3. Kaplan-Meier Plots by HIV Status.



A, Time to Urgent Coronary Revascularization. B, Time to Non-Urgent Coronary Revascularization

ACS, acute coronary syndromes; CRV, coronary revascularization; HIV, human immunodeficiency virus; HR, hazard ratio; PLHIV, people living with human immunodeficiency virus.

Figure S4. Kaplan-Meier Plot by HIV Status for Heart Failure Requiring Hospitalization at 36 months.



HIV, human immunodeficiency virus; HR, hazard ratio; PLHIV, people living with human immunodeficiency virus.