Incidence of Herpes Zoster in HIV-Infected Adults in the Combined Antiretroviral Treatment (cART) Era: Results from the FHDH-ANRS CO4 Cohort

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The risk of HZ has declined markedly among HIV1-infected patients in the cART era but remains 3 times higher than in the general population. The risk transiently and moderately increases during the first 6 months of cART.

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ABSTRACT

Background: Recent studies have shown a decrease in the incidence of herpes zoster (HZ) among HIV-infected patients since the cART era, but more data are needed on a possible increase in the risk early after cART initiation.

Methods: We studied the HZ incidence and risk factors among patients followed in the French Hospital Database on HIV (FHDH) between 1992 and 2011. Standardized incidence ratios (SIR) were used for comparison with the general population between 2005 and 2008. The risk of HZ following cART initiation (0-6, ≥6 months) was studied with Poisson regression models.

Results: 7167 cases of incident HZ were diagnosed among 91 044 individuals (583 125 person-years). The incidence declined significantly from 2955 per 100 000 person-years in 1992-1996 to 628 in 2009-2011. This decline was mainly explained by cART (RR=0.60; 95%CI, 0.57-0.64). The risk of HZ was associated with low CD4 cell counts, high HIV-RNA levels, low CD4/CD8 ratios and prior AIDS. Compared to the general population, the risk of HZ was higher in HIV-infected patients (overall SIR=2.7; 95%CI, 2.6-2.9), particularly between ages 15 and 45 years (SIR=4-6). In ART-naive patients a moderate increase in the HZ risk was observed during the first 6 months of cART, with a peak at 3 months (RR=1.47 95%CI, 1.26-1.73) a finding that disappeared after adjustment for the current CD4 cell count (RR=1.03; 95%CI, 0.81-1.32).

Conclusions: The risk of HZ has declined markedly among HIV-infected patients in the cART era but remains 3 times higher than in the general population. The risk increases moderately during the first 6 months of cART.

INTRODUCTION

Herpes zoster (HZ) is due to reactivation of latent varicella-zoster virus (VZV). It is mainly a disease of elderly and immunocompromised subjects, likely owing to impaired cell-mediated immunity [1-2]. Before the advent of combined antiretroviral treatment (cART), the incidence of HZ in HIV-1-infected patients was 10 to 30 times higher than in HIV-seronegative individuals [3-5]. In most studies, low CD4 cell counts were the most potent predictor of HZ [4, 6-8].

Since the advent of cART, most complications of HIV infection have changed dramatically in terms of their incidence and clinical presentation, but little is known of the impact of cART on the incidence of and risk factors for HZ. Although the restoration of cell-mediated immunity on cART is expected to reduce the risk of HZ, treated patients live much longer and may thus become more susceptible to HZ due to the natural decline in cell-mediated immunity associated with aging. Some cohort studies of adults [9] and children [10] suggest that the HZ incidence has not changed significantly since the advent of cART, while others show a significant decrease [7-8, 11-15]. However, HIV infection remains a significant risk factor for HZ, even in the higher CD4 cell strata (> 750/mm^3) [7]. Several studies have shown an increase in HZ incidence during the first months following cART initiation, suggesting that HZ may be a feature of the immune reconstitution syndrome (IRIS) [11, 16-17]. However, longitudinal data on the risk of HZ early after cART initiation are sparse.

As HZ is caused by VZV reactivation, VZV vaccination might help to prevent it. A live attenuated VZV vaccine is licensed in several countries for HZ prevention in persons over 50 years of age but is contraindicated in immunodeficient individuals. There are currently two candidate vaccines in development for the prevention of HZ in immunocompromised populations, including HIV-infected patients [18] .

To better inform vaccination policies in Europe, we studied the HZ incidence rate and risk factors in HIV-1-infected patients followed in the French Hospital Database on HIV (FHDH-ANRS CO4) during the years 1992-2011, by comparison with the general population during the years 2005-2008. We also studied the early impact of cART initiation in a subgroup of naïve patients.

METHODS

Study population

Patients were selected from the French Hospital Database on HIV (FHDH-ANRS CO4) [19], a nationwide hospital-based cohort created in 1989. Seventy clinical centers in hospitals across France currently contribute data on HIV-infected patients. The only FHDH inclusion criteria are HIV-1 or HIV-2 infection and written informed consent. Trained research assistants prospectively collect clinical, biological and therapeutic data at least every 6 months from medical records, using specialized softwares. Clinical events are collected using the International Classification of Diseases (ICD). The ninth revision codes were used prior to 1997 and the tenth revision thereafter. The FHDH was approved by the French data protection authority (Commission Nationale de l'Informatique et des Libertés). Patients were not eligible for this study if they were less than 15 years old, HIV-2-infected or not followed between January 1992 and December 2011, and if they had less than 6 months of follow-up, no CD4 cell count at cohort entry, or a history of VZV infection or ongoing VZV infection at cohort entry. The study was also limited to adults younger than 85 years, as fewer than 10 cases of HZ occurred beyond this age.

French general population

The Sentinelles general practitioner (GP) surveillance network provided the incidence of HZ in the background general population in France[20] in 2005-2008. This network involves about 1200 volunteer GPs who have reported weekly all cases of 10 predefined diseases, including HZ infection since 2005. The network GPs have been shown to be representative of all GPs in France.[21] Annual incidence rates are corrected for the participating GPs' geographic distribution.

Herpes zoster definition

Cases of HZ were extracted from the FHDH and Sentinelles Network by using the following (ICD) codes from the ninth and tenth revisions: 53.0-53.9 (ICD-9) and B02.0-B02.9 (ICD-10).

Statistical Analysis

Follow-up time was measured from FHDH enrollment until diagnosis of HZ, death, the last follow-up visit, or 31 December 2011, whichever occurred first. HZ incidence rates were calculated by dividing the observed number of incident HZ cases by the number of person-years (PY) at risk in each of the five following calendar periods: the pre-cART period (1992-1996) and the cART era divided into four periods: early (1997-2000), intermediate (2001-2004), late (2005-2008) and recent (2009-2011). Only first episodes of HZ were considered. To permit temporal comparisons within the HIV-infected population, HZ incidence rates (IR) and their 95% confidence intervals (CI) in each calendar period were standardized for the demographic structure (age in 5-year increments and gender) of all HIV1-infected patients followed during the cART period (1997-2011), using the direct method.

Factors associated with the risk of HZ in HIV-infected patients were identified by using Cox proportional hazard models including gender, the HIV transmission group, age at inclusion in the FHDH, sub-Saharan Africa origin, AIDS status before HZ or at the end of follow-up, the CD4 cell nadir before HZ or before the end of follow-up, the current CD4 cell count, and either cART use or the calendar period as a proxy of treatment exposure. cART was defined as a combination of 3 or more drugs or a dual therapy with two boosted PIs or one boosted PI plus one non nucleoside reverse transcriptase inhibitor; or at least one boosted PI combined with an integrase inhibitor and/or an anti-CCR5 drug; or boosted protease inhibitor monotherapy (PI), whatever the PI. The pre-cART period or the late cART period (2005-2011) was used as the reference calendar period. For continuous variables, the choice between continuous and categorical classification was based on the lowest value of Akaike's information criterion (AIC) for the corresponding univariable Cox regression model. The reference category for age was the median age class. We used the 1993 Centers for Disease Control and Prevention clinical AIDS case definition. Models restricted to patients followed after 1996, when HIV RNA assay became widely available, were adjusted for the HIV RNA level and CD4/CD8 ratio. AIDS diagnosis, the current CD4 cell count, the CD4/CD8 ratio, the HIV RNA level and cART exposure were considered as time-updated covariates.

In order to study the impact of cART on the risk of HZ early after treatment initiation and the possibility that HZ might be a manifestation of IRIS, we evaluated the risk of HZ during the first months of cART by using the same methodology as that used elsewhere for Hodgkin's lymphoma [22] and Kaposi's sarcoma [23]. For this purpose we considered a subset of antiretroviral-naive patients who either initiated cART or remained untreated. We excluded patients who had received single or dual antiretroviral regimens prior to cART. Exposure to cART and its duration in each patient were divided into the following time-interval categories: no cART and year <1996, no cART and year ≥1996 (the reference category), and first 3 months, 3 to 6 months, and more than 6 months since starting cART. The analysis used the intention-to-continue-treatment principle, i.e. did not consider changes of antiretroviral regimen. Univariable and multivariable Poisson modeling was used to study the impact of the duration of cART exposure and other variables on the incidence (risk) of HZ. The first multivariable model (MV0) was adjusted for age, gender and the HIV transmission group, sub-Saharan origin, and AIDS status. In two other multivariable models, to the variables included in MV0 we added the current CD4 cell count (MV1), and the current CD4 cell count plus the current pHIV RNA level (MV2).

To compare the risk of HZ between the HIV-infected population and the general population in France in 2005-2008, we calculated standardized incidence ratios (SIR), which reflect the risk of HZ in HIV-infected patients relative to the general population, if the general population was demographically similar to the HIV population. SIRs were calculated by dividing the observed number of cases of incident HZ among HIV-infected patients by the expected number. Expected numbers of HZ cases were obtained by multiplying patient-years at risk in each 5-year age group of the HIV-infected population by the corresponding sex- and age-specific incidence rates in the general population.

SAS software version 9.3 (SAS Institute, Cary, NC) was used for all statistical analyses.

RESULTS

Patients

Between 1992 and 2011, 91 044 HIV-infected patients from the FHDH cohort were eligible for the study and contributed 583 125 PY at risk of HZ. An incident HZ was diagnosed in 7167 patients (**Figure 1**). Characteristics of the patients with and without incident HZ are described in **Table 1**.

Most patients with HZ were men (72%), and median age was 38 years. MSM accounted for 39.6% of the HZ patients. The median CD4 cell count at HZ diagnosis was 304/mm^3 (nadir 176/mm^3). Patients with HZ were less likely than patients without HZ to have pHIV RNA below 500 cp/ml (28.7% versus 69.3%).

HZ incidence rate and risk factors

Figure 2 shows the incidence rate of HZ according to the calendar period, CD4 cell count, CD4/CD8 ratio, and HIV RNA level. The incidence rate declined significantly over the study period (p for trend <0.0001 in both men and women) from 2955 per 100 000 person-years (PY) in 1992-1996 to 628 per 100 000 PY in 2009-2011, and continued to decline during the cART period (p for trend p<0.0001). Higher incidence rates of HZ were found in men, patients with low CD4 cell counts and low CD4/CD8 ratios, and patients with high pHIV RNA levels.

In multivariable analyses **(Table 2)**, the risk of HZ was associated with age at FHDH entry, women gender and the transmission group, geographic origin (lower rates in sub-Saharan patients), AIDS status, the CD4 cell nadir, both the current and nadir CD4 cell count, cART use, and the calendar period. Compared with the period 1992-1996, a significant decline in the risk of HZ was found in 2009-2011 (-66%). This decrease continued steadily during the cART period, with an RR of 0.8 (95%CI, 0.72-0.88) in 2009-2011 compared to 2005-2008. In the model adjusted for cART instead of the calendar period (Supplementary Table 2), the risk associated with exposure to cART was RR=0.60 (95%CI, 0.57-0.64). Among patients enrolled after 1997, 5122 incident cases of HZ occurred and multivariable models (**Table 2**, Model 2) indicated that the HIV RNA level and CD4/CD8 ratio were also significantly associated with the risk of HZ: HZ was more likely to occur in patients with higher HIV RNA levels and in patients with CD4/CD8 ratios below 0.9.

Risk of IRIS

A total of 48 616 initially ART-naive patients were included in the analysis of the early impact of cART on the HZ incidence. In this subpopulation, 2654 incident cases of HZ occurred in median in 2001-2004, at a median CD4 cell count of 363/mm^3 (IQR, 218-521). Of these, 1621 cases occurred in patients on cART, 368 (24%) during the first 6 months of cART. Among cART-naive patients, the HZ incidence was 1131/100 000 person-years (PY) prior to 1996. After 1996, the incidence was maximal at 2275/100 000 PY during the first 3 months of cART, and declined to 742/100 000 PY after 6 months of cART. The RR derived from Poisson regression models are given in **Table 3**. As compared to untreated patients during the years 1996-2011, the crude risks of HZ were significantly elevated during the first 6 months of cART, with a RR reaching 1.58 (95%CI, 1.35-1.84) at 3 months of cART, then declined markedly after 6 months: RR=0.51 (95%CI, 0.47-0.56). Adjustment for the current CD4 cell count reduced the RR during the first 3 months to close to 1 (RR=0.94, 95%CI, 0.80-1.10), additional adjustment for HIV RNA showed a persistent

moderate and statistically significant increase between 3-6 months RR = 1.39 (95%CI, 1.16-1.66). Restriction to a population followed after 1997 with available HIV RNA measures gave very similar estimates (not shown).

Comparison with the general population

In the general population in 2005-2008, HZ occurred at a median age of 60 years and was more frequent in women than in men. The crude incidence rate was 439 per 100 000 PY in women and 351 per 100 000 PY in men. Contrary to the HIV-infected population, the incidence increased significantly with age in the general population (**Figure 3-panel A).** After accounting for the gender and age structure of HIV-infected population, the risk of HZ was 2.7 times higher in the HIV-infected population than in the general population (overall SIR=2.7 95%CI, 2.6-2.9). In both men and women**,** the SIRs were highest at the youngest ages (**Figure 3-panel B**) and declined significantly across the age groups (p=0.003 for trend). SIRs were no longer significantly different from those in the general population after 65 years of age.

DISCUSSION

This study of a large population of HIV-infected patients shows that the incidence rate of HZ in France declined significantly with the advent of cART and that it continued to decline thereafter, reaching 628/100 000 PY in 2009-2011. However, the risk of HZ in HIV-infected patients remains roughly 3 times higher than in the general population, particularly in the 15- to 45-year age group, in which the excess risk is 6-fold. The risk of HZ was associated with the degree of immune deficiency and was greatly reduced by cART. In addition, among antiretroviral-naive patients, we found that the risk of HZ increased moderately during the first months of cART, before falling sharply thereafter.

Strengths and limits

The main strengths of our study are the very large size of the study population, the prospective follow-up in both the pre-cART and cART eras, the lengthy follow-up in the cART era (518 764 PY), and comparison with the general population. One limitation is that although HZ is classified as a class B clinical manifestation of HIV infection in the CDC classification, milder HZ episodes may have been underreported in the FHDH cohort, leading to an underestimation of the incidence rates. However, this underreporting is likely stable over time and would not therefore have markedly affected the observed time trends. HZ symptoms and complications such as post-herpetic neuralgia are not studied in detail in the FHDH cohort, as this would require the use of a specific questionnaire.

Temporal trends of HZ incidence and risk factors in HIV-infected patients

We found that the incidence of HZ in HIV-infected patients declined over time, from 2955/100 000 PY in pre-cART period to 845/100 000 PY in 2005-2008. The incidence rate continued to decline significantly during the cART era. Most recent studies[3, 13] have shown similar trends, although some earlier reports indicated no change in the risk of HZ since the cART era[9, 24]. In our Cox multivariable model, cART was associated with a 40% decrease in the risk of HZ. Like others[7, 13-15], we found a clear association between the CD4 cell count and the risk of HZ. The severity of immune depression, reflected by the current CD4 cell count, the CD4 cell nadir, AIDS status, and current viral load, was also associated with the risk of HZ. Interestingly, we found an inverse dose-response relationship between the CD4/CD8 ratio and the risk of HZ, independently of the CD4 cell count and viral load. An association between the CD8 cell count and the risk of HZ has also been described by others [16-17]. Overall, our results suggest that the decrease in the incidence of HZ in the cART era is due to immune restoration and viral control.

IRIS

IRIS has been associated with a plethora of health disorders, including HZ. The lack of standardized IRIS definitions makes it difficult to compare the results across studies. The IRIS phenomenon is also difficult to analyze in studies that are not specifically designed to prospectively collect relevant information. A meta-analysis of the risk of IRIS in patients starting cART[25] identified only one study[26] that reported the risk of HZ in this context: 12.2% of patients initiating cART developed HZ. More recently, Blank et al[15] found a 4-fold higher risk of HZ during the first 3 months of

cART in the US and a study from South Africa[27] found a 1-year incidence rate of 1810/100 000PY after starting cART. Our data indicate that the risk of HZ is moderately elevated in the first 6 months of cART (adjusted RR=1.5), with a peak just before the third month of treatment. After 6 months of cART, the risk fell sharply by 40% compared to untreated patients. Surprisingly, in naïve-patients pre-cART RRs were lower than post-cART RRs except after 6 months of cART. Although there was no clear explanation for that neither an indication bias with cART being given to patients more at-risk of HZ nor an under-notification of HZ in the precART with more severe diseases competing patients prognosis in the pre-cART era cannot be excluded.

Comparison with the general population

In the general population, the incidence of HZ increases with age and is higher in women[20]. By comparison with the general population, after accounting for differences in the gender and age distribution, we found that the risk of HZ was 2.7 times higher in the HIV-infected population. This excess risk was higher at younger ages and maximal between 15 to 34 years, when it approached 6-fold and was no longer significant over 65 years of age. Other studies, comparing the risk to that of either a general population or an HIV-uninfected population,[7] also showed a higher risk in HIV-infected individuals. In other immunocompromised individuals, with cancer[28] or systemic lupus erythematosus[29] for example, acquired or treatment-induced immunodeficiency is also associated with an increased risk of HZ. In the study by Kaiser Permanente Northern California [28], the risk of HZ was 4.8 times higher in patients with hematologic malignancies and 1.9 times higher in those with solid tumors than in the U.S. general population. A U.S. Veterans cohort [13] showed that the incidence of HZ decreased with increasing age in HIV-infected individuals, whereas it increased with age in the general veteran population [30]. Taking together, the increased risk observed here in the younger strata of HIV-infected patients, suggests that the benefits and safety of VZV vaccination should be studied in HIV-infected individuals below the age recommended for vaccination in the general population.

CONCLUSIONS

The overall decrease in the incidence of herpes zoster among HIV-infected patients in the cART era is probably related to improved immune restoration and viral control. This trend may continue in future as cART is initiated earlier, at higher CD4 cell counts, as recommended in most recent guidelines. However, clinicians and patients should be aware that cART transiently increases the risk of HZ during the first 6 months of treatment.

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POTENTIAL CONFLICTS OF INTEREST:

None of the authors has any financial or personal relationships with people or organizations that could inappropriately influence this work, although several members of the group have, at some stage in the past, received funding from a variety of pharmaceutical companies for research, travel grants, speaking engagements or consultancy fees.

AUTHOR CONTRIBUTIONS:

SG, PT and OL designed the study.

HSL performed the statistical analyses.

SG, PT, DC and OL interpreted the data and wrote the manuscript.

All the authors read and critically commented on the paper.

Members of the FHDH-ANRS C04 Cohort are listed at :

http://www.ccde.fr/main.php?main_file=fl-1171464013-677.html

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Table 1 : Characteristics of HIV1-infected patients with and without incident herpes zoster in the FHDH-ANRS CO4 cohort.

	HIV-infected population in 1992-2011	
	with incident HZ (n=7 167pts)	**without HZ (83 877 pts)**
Men N(%)	5161 (72.0)	57 928 (69.1)
Age at HZ or last follow-up[¥], median (iqr)	38 (33-45)	42 (35-49)
Transmission group, N (%)		
MSM	2836 (39.6)	29122 (34.7)
IVDU	1139 (15.9)	11231 (13.4)
Others	3196 (44.5)	43524 (51.9)
Migrant from sub-Saharan Africa, N (%)	662 (9.2)	12034 (14.3)
AIDS prior to HZ or last follow-up[¥], N (%)	2143 (29.9)	23122 (27.6)
CD4 nadir[¥] **/mm³**, median (iqr)	176 (57-315)	206 (77-336)
CD4 at HZ or last follow-up*[¥]**/mm³**, median (iqr)	304 (155-465)	449 (257-646)
CD8 at HZ or last follow-up[¥]*, median (iqr)	901 (604-1275)	788 (540-1108)
CD4/CD8 at HZ or last follow-up[¥]*, median (iqr)	0.3 (0.2-0.5)	0.5 (0.3-0.9)
pHIV RNA at HZ or last follow-up[¥]*, **cp/mL** median (iqr)	3200 (157-42000)	50 (50-970)
<500	1496 (28.7)	51221 (69.3)
50-5 000	1293 (24.8)	8616 (11.7)
5 000-30 000	885 (17.0)	5817 (7.9)
≥ 30 000	1540 (29.5)	8298 (11.2)
Periods of HZ or at last visit N(%)		
1992-1996	1784 (24.9)	8738 (10.4)
1997-2000	1941 (27.1)	7014 (8.4)
2001-2004	1505 (21.0)	7522 (9.0)
2005-2008	1341 (18.7)	13107 (15.6)
2009-2011	596 (8.3)	47496 (56.6)
Duration of combined ART at HZ or last follow-up[¥] N(%)		
No cART and <1996	1146 (16.0)	6739 (8.0)
No cART and ≥ year 1996	2369 (33.1)	15568 (18.6)
cART for less than 6 months	759 (10.1)	4774 (5.7)
cART for more than 6 months	2893 (40.4)	56796 (67.7)

* 6 months before to 1 month after HZ diagnosis

¥ before diagnosis of HZ in patients with HZ and before the end of follow-up for patients without HZ

CD8 and CD4/CD8 ratio data were available for 83% and 89% of the patients with HZ between 1992-2011 and 2005-2011 respectively, and for 88% of the patients without HZ.

HIV RNA measurement became available after 1997 in the FHDH cohort; the data were thereafter available for 98% of the patients with HZ and 83% of the patients without HZ.

Abbreviations: IVDU, Intravenous drug use; MSM, Men who have sex with men; cART, combined antiretroviral treatment; FHDH, French Hospital Database on HIV;

Table 2: Risk of Herpes Zoster in HIV-infected patients. Multivariable Cox regression analysis**.**

		Model 1 Period 1992-2011 (n=7167 HZ, AIC=154 079)				Model 2 Period 1997-2011 (n=5122 HZ, AIC=106 085)**			
		HR	95%CI		P***	HR	95% CI		P***
Gender and transmission group					<.0001				<.0001
	IVDU men	0.94	0.86	1.03		0.93	0.83	1.04	
	Other men	1				1			
	MSM	1.18	1.11	1.26		1.17	1.08	1.26	
	IVDU women	1.12	0.99	1.26		1.20	1.03	1.40	
	Other women	1.10	1.02	1.18		1.14	1.05	1.24	
Age at FHDH entry					0.010				0.003
	<24 years	0.80	0.69	0.94		0.72	0.60	0.87	
	25-34	0.93	0.87	1.00		0.87	0.80	0.95	
	35-44	0.93	0.87	0.99		0.89	0.83	0.96	
	45-54	1				1			
	55-64	1.11	1.00	1.22		1.15	1.03	1.29	
	>=65	0.94	0.79	1.13		1.03	0.85	1.25	
Sub-Saharan origin	yes vs no	0.87	0.79	0.94	0.0011	0.84	0.77	0.93	0.0004
AIDS*	yes vs no	1.21	1.14	1.28	<.0001	1.24	1.16	1.33	<.0001
CD4 nadir (/mm^3)					<.0001				<.0001
	≥500	1				1			
	350 - 499	1.28	1.15	1.43		1.15	1.01	1.30	
	200 - 349	1.37	1.24	1.51		1.21	1.08	1.37	
	<200	1.59	1.44	1.77		1.44	1.27	1.64	
CD4 current* (/mm^3)	log2	0.87	0.85	0.88	<.0001	0.93	0.91	0.96	<.0001
Period*					<.0001				<.0001

	1992-1996	1			_		
	1997-2000	0.87	0.81	0.93	1		
	2001-2004	0.63	0.58	0.69	0.82	0.77 0.89	
	2005-2008	0.54	0.50	0.59	0.77	0.71 0.84	
	2009-2011	0.44	0.39	0.49	0.72	0.64 0.80	
HIV RNA current (cp/ml)*							<.0001
	<500				1		
	500-4 999				1.66	1.53 1.80	
	5 000-29 999				2.15	1.96 2.36	
	≥30 000				2.93	2.69 3.19	
CD4/CD8 ratio*							<.0001
	≥0.9				1		
	[0.5 - 0.9[				1.23	1.09 1.39	
	[0.3 - 0.5[				1.66	1.47 1.88	
	<0.3				1.86	1.64 2.12	
	missing				1.21	1.06 1.38	

*time-updated variables

[¥] before diagnosis of HZ in patients with HZ, and before the end of follow-up for patients without HZ

Abbreviation: HZ, Herpes Zoster; HR, Hazard ratio; 95%CI, 95% confidence interval; MSM, men who have sex with men;

AIC Akaïke's Information Criterion

**Model 2 concerns only patients included since 1997 when HIV RNA measurement became available

*** p-value for the overall effect of the variable

Table 3 : Relative risk of HZ according to cART use, derived from Poisson regression models in 48 616 cART-naive patients either initiating cART or remaining untreated (2654 incident HZ cases).

	Univariable model				Multivariable model 0*				Multivariable model 1**				Multivariable model 2***			
Duration of cART	RR	95%CI		p	RR	95%CI		p	RR	95%CI		p	RR	95%CI		p
no cART and year<1996	0.78	0.63	0.98	0.033	0.75	0.60	0.95	0.0145	0.68	0.54	0.86	0.001				
no cART and year≥1996	1				1				1				1			
0-3 month	1.58	1.35	1.84	<.0001	1.39	1.19	1.62	<.0001	0.94	0.80	1.10	0.4169	1.04	0.88	1.23	0.6408
3-6 months	1.47	1.26	1.73	<.0001	1.29	1.10	1.52	0.0018	0.95	0.80	1.11	0.5071	1.39	1.16	1.66	0.0003
≥6 months	0.51	0.47	0.56	<.0001	0.44	0.40	0.48	<.0001	0.41	0.37	0.45	<.0001	0.66	0.59	0.73	<.0001

*MV0 adjusted for age, gender, exposure group, sub-Saharan origin and AIDS status.

** MV1 adjusted for variables in MV0 plus current CD4 cell count (time-updated variable)

*** MV2 adjusted for variables in MV1 plus current HIV RNA (time-updated variable), which was not available until 1997.