



**HAL**  
open science

## **Predictive Factors of Herpes Zoster HIV-Infected Patients: Another Adverse Effect of Crack Cocaine.**

Mathieu Nacher, Celia Basurko, Antoine Adenis, Emilie Gaubert-Marechal, Emilie Mosnier, Sophie Edouard, Vincent Vantilcke, Sindou Sivapregassam, Benoit Tressières, André Cabié, et al.

### ► To cite this version:

Mathieu Nacher, Celia Basurko, Antoine Adenis, Emilie Gaubert-Marechal, Emilie Mosnier, et al.. Predictive Factors of Herpes Zoster HIV-Infected Patients: Another Adverse Effect of Crack Cocaine.. PLoS ONE, 2013, 8 (11), pp.e80187. 10.1371/journal.pone.0080187 . inserm-00921158

**HAL Id: inserm-00921158**

**<https://inserm.hal.science/inserm-00921158>**

Submitted on 19 Dec 2013

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Predictive Factors of Herpes Zoster HIV-Infected Patients: Another Adverse Effect of Crack Cocaine

Mathieu Nacher<sup>1,2,3\*</sup>, Celia Basurko<sup>1</sup>, Antoine Adenis<sup>1</sup>, Emilie Gaubert-Marechal<sup>3</sup>, Emilie Mosnier<sup>4</sup>, Sophie Edouard<sup>4</sup>, Vincent Vantilcke<sup>5</sup>, Sindou Sivapregassam<sup>1</sup>, Benoit Tressières<sup>6</sup>, André Cabié<sup>7</sup>, Pierre Coupié<sup>4</sup>

**1** Centre d'Investigation Clinique Epidémiologie Clinique Antilles Guyane (INSERM / DGOS CIE 802), Centre Hospitalier de Cayenne, Cayenne, French Guiana, **2** Epidemiologie Parasitoses et Mycoses Tropicales, EA 3593, Université Antilles Guyane, and COREVIH Guyane, Cayenne, French Guiana, **3** Centre Hospitalier de Cayenne, Cayenne, French Guiana, **4** Service de Dermatologie Vénérologie, Centre Hospitalier de Cayenne, Cayenne, French Guiana, **5** Service de Médecine, Centre Hospitalier Franck de l'Ouest Guyanais, Saint-Laurent-du-Maroni, French Guiana, **6** Centre d'Investigation Clinique Epidémiologie Clinique Antilles Guyane (INSERM / DGOS CIE 802), Centre Hospitalier Universitaire de la Martinique, Fort de France, Martinique, France, **7** Service de Maladies Infectieuses et Tropicales, Centre Hospitalier Universitaire de la Martinique, Fort de France, Martinique, France

## Abstract

A retrospective cohort study was conducted on 1541 HIV-infected patients to determine variables associated with the incidence of herpes zoster. A single failure Cox model showed that herpes zoster incidence increased following the first 6 months of antiretroviral treatment adjusted hazard ratio (AHR)=5 (95%CI=2.6-9.2),  $P<0.001$ ; in the >60 years age group AHR=2 (95%CI=1-4),  $P=0.04$ ; in patients in the top CD8 quartile AHR=2.1 (95%CI=1.3-3.6),  $P<0.001$ ; and in patients previously reported to use crack cocaine AHR=5.9, (95%CI=1.4-25),  $P=0.02$ . Herpes zoster incidence increased in patients with CD4 counts<500 per mm<sup>3</sup> and gradually declined since 1992-1996, with AHR=0.3 (95%CI=0.2-0.5),  $P<0.001$  for the 1997-2002 period and AHR=0.24 (95%CI=0.14-0.4),  $P<0.001$  for the 2002-2008 period. Contrary to what has been described elsewhere, there was no specific effect of protease inhibitors on herpes zoster incidence. The present study is the first to suggest that crack cocaine is associated with an increased incidence of herpes zoster. The neurological or immunological effects of crack are discussed.

**Citation:** Nacher M, Basurko C, Adenis A, Gaubert-Marechal E, Mosnier E, et al. (2013) Predictive Factors of Herpes Zoster HIV-Infected Patients: Another Adverse Effect of Crack Cocaine. PLoS ONE 8(11): e80187. doi:10.1371/journal.pone.0080187

**Editor:** Qiliang Cai, Fudan University, China

**Received:** July 9, 2013; **Accepted:** September 28, 2013; **Published:** November 11, 2013

**Copyright:** © 2013 Nacher et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Funding:** No current external funding sources for this study.

**Competing interests:** The authors have declared that no competing interests exist.

\* E-mail: mathieu.nacher@ch-cayenne.fr

## Introduction

Similar to other herpes viruses, the varicella-zoster virus (VZV) causes both acute illness and lifelong latency. During the primary infection, VZV enters the cutaneous endings of sensory nerves and migrates up to the sensory nerve ganglia. The virus incorporates nucleoprotein within ganglionic cells and establishes latency which is maintained through cellular immunity [1]. With advancing age, VZV-specific cellular immunity weakens and the virus may be reactivated and migrate along the sensory nerves to reach the corresponding dermatoma. Other causes of immunodepression, such as HIV infection, may lead to the same consequences[2]. The occurrence of herpes zoster does not reliably predict the immunovirological progression of HIV infection. Several studies have suggested that incidence remained fairly stable at any stage of the HIV infection[3-5]. However, others have suggested that incidence was greater when immunosuppression worsened[3,6,7]. Several authors also reported that herpes zoster incidence transiently increased

following antiretroviral therapy initiation thus representing a common form of immune reconstitution disease [8-11]. It was notably reported that protease inhibitors, perhaps because of their specific boosting effect on CD8 counts[12,13], were associated with a greater incidence of herpes zoster[8].

In acute VZV infection, varicella, primarily affects children in temperate areas. Thus most HIV-infected patients born in the United States and Europe have already had varicella or have been vaccinated, and therefore are not susceptible to primary infection. However, in tropical areas children often escape primary infection [14]. The objective of the present study was to determine the incidence and the predictive factors of Herpes zoster in a cohort of ethnically diverse patients followed in French Guiana.

## Methods

### HIV in French Guiana

French Guiana is the French territory where the HIV prevalence is highest. The epidemic is driven by transactional sex and perhaps by crack cocaine. Over seventy percent of the patients are foreign (from Haiti, Suriname, Brazil, Guyana, Dominican republic and other countries). The health system is the French system. All patients residing for over 3 months on the territory are eligible to receive health insurance and residence permits. The latest antiretrovirals, genotyping, viral load and other biological tests are free of charge.

### Patients

All HIV-positive patients followed in Cayenne, Kourou, and Saint Laurent du Maroni Hospitals between 1 January 1992 and 31 October 2008 were enrolled in the French Hospital Database for HIV (FHDH). Time-independent variables such as sex, nationality, mode of acquisition of HIV, and time-dependent variables such as age, CD4 cell counts, CD8 counts, HIV-1 viral loads, antiretroviral treatments, and clinical events are routinely entered by trained clinical studies technicians. Diagnoses are coded according to the 10th International Classification of Diseases. Specific details such as the location of herpes zoster could not be obtained from the database.

### Ethical and Regulatory aspects

Patients included in the FHDH give written informed consent for the use of their records' data. Their identity is encrypted before the data are sent to the Ministry of Health and the Institut National de la Recherche Médicale, which centralizes data from Regional coordination committees for the fight against HIV/AIDS (COREVIH) throughout France. This data collection is approved by the Commission Nationale Informatique et Libertés.

### Study design

The study was a retrospective cohort study, using a single failure Cox proportional hazards model to evaluate the adjusted relationship between failure and explanatory variables. The failure event was the incidence of a first episode of herpes zoster. The main explanatory variables were age categorized (<30, 30-39, 40/59, >60), sex, nationality, reported addictions, CD4 cell count at the time of the visit (categorized as <50, 50–199, 200–499, and >500 cells/ml), CD8 cell count categorized in 4 quartiles (<642, 642-949, 950-1362, >1362), HIV1 viral load, the presence or absence of HAART, the time since treatment started (<6 months, >6 months), and the period (1992-1996, 1997-2002, 2003-2008). The proportionality of the hazard functions was determined using Schoenfeld and scaled Schoenfeld residuals and the global proportional hazards test. Age, CD4 and CD8 cell count category at the time of HIV diagnosis, and follow-up duration were transformed into dummy variables to compare different groups with a reference group.

In order to test the eventual influence of protease inhibitors, 2 approaches were used: first, an interaction term between the 6 month period following treatment initiation and protease inhibitors was created and added to the Cox model.; second, a nested case control study was conducted with 4 random controls sampled for each case of herpes zoster, at the time of herpes zoster. The data were analysed using STATA 12.0 (STATA Corp., College Station, Texas, USA).

## Results

A total of 1541 subjects with 34310 observations were included, representing a total of 7159 person-years of follow-up. A total of 181 first clinical episodes of herpes zoster were recorded. There were 2 reported cases of meningeal herpes zoster, and 7 cases of disseminated herpes zoster. Table 1 shows the crude incidence rates and the adjusted hazard ratios for a first episode of herpes zoster. The overall incidence rate of herpes zoster was 2.2 per 100-person years. However, it increased during the 6 months following treatment initiation. Incidence progressively declined between 1992-1996 period, the 1997-2002 period, and the 2003-2008 period.

After adjusting for potential confounders, such as antiretroviral treatment, CD4 counts, age and gender, this association remained significant. The interaction term testing a specific effect of protease inhibitors on the incidence of herpes zoster was not significant, thus removed from the final model. Similarly, the nested case control study did not find any specific association between protease inhibitors and herpes zoster (adjusted odds ratio=0.8 (95% CI=0.4-1.4),  $P=0.4$ ).

The CD4 decline was rapidly associated with an increased incidence of herpes zoster (<500 CD4 per mm<sup>3</sup>), but further immunosuppression only marginally increased the incidence of herpes zoster. Patients with CD8 counts in the 2<sup>nd</sup> and 4<sup>th</sup> quartiles had an increased incidence of herpes zoster.

Patients aged 60 and over had an increased risk of herpes zoster.

Although there were few patients concerned (n=58), there was an association between crack cocaine use and herpes zoster (incidence rate 4.4 per 100 person-years when crack use was reported versus 2.2 per 100 person years when crack use was not reported. Table 2 shows the age-stratified incidences for crack users and non users. The nadir median CD4 count was not significantly different between crack users (133.5/mm<sup>3</sup> (inter quartile range=241)) and non users (163/mm<sup>3</sup> (SD=253)),  $P=0.56$ . CD8 counts at the same time were significantly lower among crack users (516/mm<sup>3</sup> (inter quartile range=590)) than non users (763/mm<sup>3</sup> (inter quartile range=668)),  $P=0.005$ . After controlling for CD4 count, crack users (failure event in this model) were less likely to be on ARV treatment than non crack users adjusted hazard ratio=0.17 (0.08-0.36),  $P<0.001$ . Finally, the Analysis of the proportion of crack users by period showed that there was a gradual increase in the proportion of crack users 1.1% in 1992-1996, 1.8% in 1997-2002, and 5.8 in 2002-2008 ( $P<0.001$ ).

**Table 1.** Predictive factors of herpes zoster in HIV patients in French Guiana.

Variable	Incidence rate per 100 person-years		Adjusted hazard ratio (95% confidence interval)	P
	Incidence rate	Adjusted hazard ratio		
<b>CD4 count</b>				
[0-50]	2.4	3.5	(1.5-8.2)	0.004
]50-200]	3.1	4.2	(2.2-8)	<0.001
]200-350]	2.3	3	(1.6-5.9)	0.001
]350-500]	2	2.7	(1.4-5.3)	0.003
>500	0.9	Ref		
<b>CD8 count</b>				
[0-641]	1.3	Ref		
]642-949]	2.3	1.8	(1.06-3)	0.03
]950-1362]	1.8	1.2	(0.7-2.2)	0.4
>1362	2.9	2.1	(1.3-3.6)	<0.001
<b>Sex</b>				
Male	2	0.9	(0.7-1.1)	0.3
Female	2.1	Ref		
<b>Age group</b>				
<30	2	Ref		
]30-40]	2	1.2	(0.7-2)	0.5
]40-60]	2.1	1.2	(0.7-2)	0.5
>60	3.3	2	(1-4)	0.04
<b>Period relative to HAART initiation</b>				
Before HAART	2.2	Ref		
First 6 months of HAART	6.3	5	(2.6-9.2)	<0.001
More than 6 months of HAART	1.8	1.4	(0.8-2.1)	0.16
<b>Nucleoside &amp; nucleotide inhibitors</b>				
Yes	1.7	0.58	(0.4-0.8)	0.001
No	2.6	Ref		
<b>Protease inhibitors</b>				
Yes	1.7	0.85	(0.4-1.7)	0.6
No	2.2	Ref		
<b>Non nucleoside inhibitors</b>				
Yes	1.3	0.85	(0.4-1.5)	0.6
No	2.26	Ref		
<b>Reported crack cocaine use</b>				
Yes	4.4	5.9	(1.4-25)	0.02
No	2.1	ref		
<b>Period</b>				
1992-1996	5.3	Ref		
1997-2002	2.1	0.3	(0.2-0.5)	<0.001
2002-2008	1.3	0.24	((0.14-0.4)	<0.001

doi: 10.1371/journal.pone.0080187.t001

**Table 2.** Age-specific incidence rate of herpes zoster for crack users and non users.

Age group	Proportion of crack users (%)	Herpes zoster age-specific incidence rate for crack users (per 100 person years)	Herpes zoster age-specific incidence rate for non crack users (per 100 person years)
		<30	1.95
]30-40]	3.9	2.4	2.4
]40-60]	2.7	7.2	3.2
>60	0.7	89 (2 patients only)	4.4

doi: 10.1371/journal.pone.0080187.t002

## Discussion

Although French Guiana is in the tropics where the proportion of persons infected by VSV is lower[14], the reported incidences of herpes zoster in HIV patients were of similar magnitude as the incidences described in the USA and Spain [2,8,15-17]. The incidence tended to decrease since the years before HAART was available, as described elsewhere[18]. The incidence of herpes zoster transiently increased following antiretroviral therapy initiation, and was associated with increased age and increased CD8 count as described by others [8,9,11,19]. The incidence of herpes zoster seemed to increase for CD4 counts <500 per mm<sup>3</sup> but more advanced immunosuppression did not seem to further increase incidence. It has been reported that protease inhibitor initiation specifically increased incidence of herpes zoster, possibly through a CD8 boosting mechanism[8]. In the present study we could not replicate the same finding. It is possible that at the time of that study, protease inhibitors were the main antiretrovirals that led to virological suppression and immune reconstitution. The important aspect was the virological suppression rather than the specific action of protease inhibitors. Here we observed that overall, nucleoside and nucleotide inhibitors, the backbone of most HAART regimens, were associated with an overall reduction of herpes zoster incidence. The exact pathophysiology of herpes zoster as an immune reconstitution event is not clear. First the immune restoration may lead to increased viral excretion followed by increased incidence of clinical herpes zoster. Another hypothesis, which should be tested, would be that herpes zoster is asymptotically excreted in some patients and that the immune reconstitution following HAART leads to patent symptoms where viruses are excreted.

The observation that crack cocaine was associated with an increase in the incidence of herpes zoster was a novel finding. Cocaine, a sigma1 agonist neurotropic drug, has an effect on the homeostatic balance between TH1 pro-inflammatory versus TH2 anti-inflammatory balance and skews the cytokine response towards anti-inflammatory cytokines[20]. Thus, a hypothesis would be that the immunomodulatory effects of cocaine would further increase viral excretion in patients already immunocompromised by HIV leading to herpes zoster. It has been reported that crack was associated with increased incidence of herpes [21], the present observation could also

reflect a similar effect on another virus from the herpes virus family. Although the results were statistically significant, the numbers were small, therefore the findings should be replicated in larger series.

## References

- Mahalingam R, Wellish M, Wolf W, Dueland AN, Cohrs R et al. (1990) Latent varicella-zoster viral DNA in human trigeminal and thoracic ganglia. *N Engl J Med* 323: 627-631. doi:10.1056/NEJM199009063231002. PubMed: 2166914.
- Buchbinder SP, Katz MH, Hessel NA, Liu JY, O'Malley PM et al. (1992) Herpes zoster and human immunodeficiency virus infection. *J Infect Dis* 166: 1153-1156. doi:10.1093/infdis/166.5.1153. PubMed: 1308664.
- Alliegro MB, Dorrucchi M, Pezzotti P, Rezza G, Sinicco A et al. (1996) Herpes zoster and progression to AIDS in a cohort of individuals who seroconverted to human immunodeficiency virus. Italian HIV Seroconversion Study. *Clin Infect Dis* 23: 990-995. doi:10.1093/clinids/23.5.990. PubMed: 8922791.
- Glesby MJ, Moore RD, Chaisson RE (1993) Herpes zoster in patients with advanced human immunodeficiency virus infection treated with zidovudine. Zidovudine Epidemiology Study Group. *J Infect Dis* 168: 1264-1268. doi:10.1093/infdis/168.5.1264. PubMed: 8228361.
- Rogues AM, Dupon M, Ladner J, Ragnaud JM, Pellegrin JL et al. (1993) Herpes zoster and human immunodeficiency virus infection: a cohort study of 101 coinfecting patients. Groupe d'Epidemiologie clinique du SIDA en aquitaine. *J Infect Dis* 168: 245. doi:10.1093/infdis/168.1.245. PubMed: 8515121.
- Veenstra J, Krol A, van Praag RM, Frissen PH, Schellekens PT et al. (1995) Herpes zoster, immunological deterioration and disease progression in HIV-1 infection. *AIDS* 9: 1153-1158. doi:10.1097/00002030-199510000-00006. PubMed: 8519451.
- Engels EA, Rosenberg PS, Biggar RJ (1999) Zoster incidence in human immunodeficiency virus-infected hemophiliacs and homosexual men, 1984-1997. District Of Columbia Gay Cohort Study. Multicenter Hemophilia Cohort Study. *J Infect Dis* 180: 1784-1789. doi:10.1086/315146. PubMed: 10558932.
- Martinez E, Gatell J, Morán Y, Aznar E, Buira E et al. (1998) High incidence of herpes zoster in patients with AIDS soon after therapy with protease inhibitors. *Clin Infect Dis* 27: 1510-1513. doi:10.1086/515019. PubMed: 9868668.
- Domingo P, Torres OH, Ris J, Vazquez G (2001) Herpes zoster as an immune reconstitution disease after initiation of combination antiretroviral therapy in patients with human immunodeficiency virus type-1 infection. *Am J Med* 110: 605-609. doi:10.1016/S0002-9343(01)00703-3. PubMed: 11382367.
- Aldeen T, Hay P, Davidson F, Lau R (1998) Herpes zoster infection in HIV-seropositive patients associated with highly active antiretroviral therapy. *AIDS* 12: 1719-1720. PubMed: 9764795.
- Ratnam I, Chiu C, Kandala NB, Easterbrook PJ (2006) Incidence and risk factors for immune reconstitution inflammatory syndrome in an ethnically diverse HIV type 1-infected cohort. *Clin Infect Dis* 42: 418-427. doi:10.1086/499356. PubMed: 16392092.
- Cuda R, Grossi CE, Whitley RJ, Tilden AB (1987) Analysis of immune function in herpes zoster patients: demonstration and characterization of suppressor cells. *J Immunol* 138: 1229-1233. PubMed: 3027175.
- Carr A, Emery S, Kelleher A, Law M, Cooper DA (1996) CD8+ lymphocyte responses to antiretroviral therapy of HIV infection. *J Acquir Immune Defic Syndr Hum Retroviro* 13: 320-326. doi:10.1097/00042560-199612010-00004. PubMed: 8948369.
- Molton J, Smith C, Chaytor S, Maple P, Brown K et al. (2010) Seroprevalence of common vaccine-preventable viral infections in HIV-positive adults. *J Infect* 61: 73-80. doi:10.1016/j.jinf.2010.04.004. PubMed: 20403382.
- Blank LJ, Polydefkis MJ, Moore RD, Gebo KA ( Oct 12012) Herpes zoster among persons living with HIV in the current antiretroviral therapy era. *J Acquir Immune Defic Syndr* Oct 1;61(2): 203-207. doi:10.1097/QAI.0b013e318266cd3c. PubMed: 22766968.
- Gebo KA, Kalyani R, Moore RD, Polydefkis MJ (2005) The incidence of, risk factors for, and sequelae of herpes zoster among HIV patients in the highly active antiretroviral therapy era. *J Acquir Immune Defic Syndr* 40: 169-174. doi:10.1097/01.qai.0000178408.62675.b0. PubMed: 16186734.
- Wood SM, Shah SS, Steenhoff AP, Rutstein RM (2008) Primary varicella and herpes zoster among HIV-infected children from 1989 to 2006. *Pediatrics* 121: e150-e156. doi:10.1542/peds.2007-2022IIIIII. PubMed: 18086820.
- Moanna A, Rimland D (2013) Decreasing incidence of herpes zoster in the highly active antiretroviral therapy era. *Clin Infect Dis* 57: 122-125. doi:10.1093/cid/cit165. PubMed: 23487391.
- Murdoch DM, Venter WD, Feldman C, Van Rie A (2008) HIV immune reconstitution syndrome in sub-Saharan Africa. *AIDS* 22: 1689-1690. doi:10.1097/QAD.0b013e328308de33. PubMed: 18670236.
- Cabral GA (2006) Drugs of abuse, immune modulation, and AIDS. *J Neuroimmune Pharmacol* 1: 280-295. doi:10.1007/s11481-006-9023-5. PubMed: 18040805.
- Nacher M, Adenis A, Hanf M, Adriouch L, Vantilcke V et al. (2009) Crack cocaine use increases the incidence of AIDS-defining events in French Guiana. *AIDS* 23: 2223-2226. doi:10.1097/QAD.0b013e32833147c2. PubMed: 19752716.

## Author Contributions

Conceived and designed the experiments: MN PC. Performed the experiments: MN. Analyzed the data: MN CB AA SS BT. Wrote the manuscript: MN EGM EM VV SE AC.