Early impact of cART on the risk of Herpes Zoster. *Results from the FHDH-ANRS CO4.*

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French Hospital Database on Hiv

BACKGROUND

Recent studies evidenced a decrease in Herpes Zoster (HZ) incidence in the cART era, although HZ has been associated with the emergence of immune reconstitution inflammatory syndrome (IRIS) in patients with late initiation of cART. However evidences are lacking on large longitudinal data on the early impact of cART initiation on the risk of HZ.

OBJECTIVES

- To study the early impact of cART initiation on the risk of HZ in a subgroup of patients naïve of ART treatment, who either initiated a cART or remained untreated.

PATIENTS & METHODS

The French Hospital Database on HIV (FHDH)

- Set-up in 1989, currently includes patients followed in 70 hospitals in France.
- FHDH inclusion criteria: to have a confirmed HIV-1 or HIV-2 infection, to be followed in an hospital and to have signed an informed consent.
- Data are collected prospectively by trained research assistants from medical records on standardized f/up on DMI2/Nadis/DIAMG softwares

Herpes zoster definition

➢ Cases of Herpes zoster (HZ) were extracted from the FHDH using the following International Classification of Diseases (ICD) codes: 53.0-53.9 (ICD-9) + B02.0-B02.9 (ICD-10).

➢ Only incident HZ were considered.

Patients

➢ HIV1-infected adults aged <85 years, ARV naïve who either initiated a cART or remained untreated. (**Fig. 1**)

➢ Those who had received single or dual antiretroviral medications prior to cART were excluded.

Statistical analysis

- Univariate and multivariate Poisson models were used to study the effects of duration of cART exposure on the risk of HZ.
  - **MV0** was adjusted for age, sex and transmission group, sub-Saharan origin (yes/no), AIDS.
  - **MV1** was adjusted for variables in MV0 **+ current CD4*** (<200, 200-349, 350-499, ≥500 /mm³)
  - **MV2** was adjusted for variables in MV0 **+ current CD4* + current pHIV RNA*** (<500, 500-4999, 5000-29999, ≥30000 cp/mL).

  *Time dependent variables
- Use and duration of cART for each patient was divided as follows: no cART and year<1996, no cART and year≥1996 (ref.), 0 to 3 months, 3 to 6 months, ≥ 6 months.
- Intention to continue treatment principle, ie did not consider the change of antiretroviral drug

RESULTS

Fig. 1: Patients flow chart

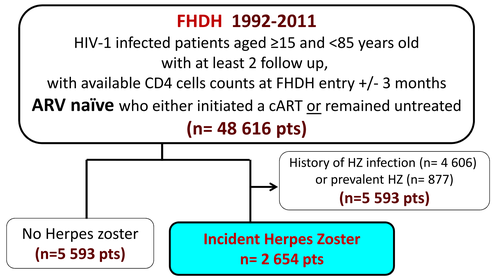


Table 1 : Characteristics of patients with incident Herpes zoster (n=2 654 pts)

Men N(%)	**1868 (70.4)**
Age at HZ, median (iqr)	**39 (33-47)**
Transmission group, N (%) MSM	994 (37.5)
IVDU	228 (8.5)
Others	1432 (54.0)
Migration from Sub-Saharan Africa, N (%)	379 (14.3)
AIDS prior to HZ, N (%)	**640 (24.1)**
CD4 at HZ*, median (iqr)	**366 (218-530)**
CD4 nadir, median (iqr)	248 (95-389)
CD4 at cART initiation median (iqr)	242 (120-355)
CD8 at HZ*, median (iqr)	**945 (659-1295)**
CD4/CD8 at HZ*, median (iqr)	**0.4 (0.2-0.6)**
pHIV RNA at HZ*, log median (iqr)	**3.66 (1.92-7.71)**
pHIV RNA at cART*, log median (iqr)	4.92 (4.39-5.42)
Periods N(%) 1992-1996	154 (5.8)
1997-2000	542 (20.4)
2001-2004	794 (29.9)
2005-2008	789 (29.7)
2009-2011	375 (14.1)

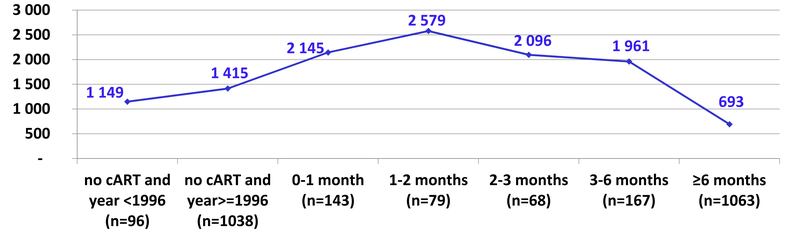
*6 months before to 1 month after HZ diagnosis
iqr: interquartile range

- A total of 2654 pts had an incident HZ during 256 491 person-years of follow-up.
- 1520 HZ occured in pts on cART, 290 (19.0%) in the first 3 months and 379 (30%) in the first 6 months (**Table 2**).

Table 2 : Frequency of incident Herpes Zoster

	N	% among patients initiating a cART
no cART and year<1996	96	
no cART and year≥1996	1 038	
0-1 month	143	9.4%
1-2 months	79	5,2%
2-3 months	68	4,5%
3-6 months	167	11,0%
≥6 months	1 063	69.9%

Fig 2. : Crude incidence of Herpes zoster according to use and duration of cART /100 000 Person-Years



- In cART naive patients, HZ incidence was 1149/10⁵ PY prior 1996. After 1996, the incidence was 2127 /10⁵ PY in the first 6 months of cART and declined to 693/10⁵ PY after 6 months of cART (see **Fig .2**).
- Poisson multivariate analyses showed that higher risk of HZ was associated with low CD4 and high HIV RNA levels, low CD4/CD8 rate and prior AIDS and age (not shown).

Table 3: RR of Herpes zoster derived from Poisson models according to use and duration of cART.

	UNIV				MV0				MV1=MV0+T4				MV2=MV0+T4+VL			
	RR	95%CI		p	RR	95%CI		p	RR	95%CI		p	RR	95%CI		p
no cART and year<1996	**0.81**	0.66	1.00	0.0512	**0.79**	0.64	0.98	0.0294	**0.73**	0.59	0.90	0.0038				
no cART and year≥1996	**1**				**1**				**1**				**1**			
0-1 month	**1.52**	1.27	1.81	<.0001	**1.36**	1.14	1.62	0.0006	**0.92**	0.77	1.11	0.3900	**0.94**	0.78	1.14	0.52
1-2 months	**1.82**	1.45	2.29	<.0001	**1.62**	1.29	2.04	<.0001	**1.16**	0.92	1.47	0.1986	**1.51**	1.19	1.92	0.00
2-3 months	**1.48**	1.16	1.89	0.0017	**1.31**	1.03	1.68	0.0294	**0.98**	0.76	1.25	0.8528	**1.34**	1.03	1.74	0.03
3-6 months	**1.39**	1.18	1.63	<.0001	**1.22**	1.04	1.44	0.0174	**0.94**	0.79	1.11	0.4416	**1.47**	1.23	1.75	<.0001
≥6 months	**0.49**	0.45	0.53	<.0001	**0.42**	0.38	0.45	<.0001	**0.40**	0.37	0.44	<.0001	**0.65**	0.58	0.73	<.0001

- As compared to untreated patients during years 1996-2011, the RR of HZ were significantly elevated in the first 6 months of cART then declined markedly after 6 months (see **Table 3**).

CONCLUSIONS

The risk of HZ increases in the first months of cART initiation but only moderately while it sharply decreases after 6 months of cART. The overall decrease in incidence after cART is probably related to immune restoration and virological control.