Lower Incidence of Cervical Intraepithelial Neoplasia (CIN) in HIV-positive women under Haart

Isabelle HEARD[1], Valérie POTARD[2], Dominique COSTAGLIOLA[2], Michel KAZATCHKINE[1]

[1] Inserm U430 and Hospital Européen G. Pompidou, [2] Inserm U720, Université Pierre et Marie Curie, Paris, France

HEGP, 20 rue Leblanc - 75015 PARIS, France - Tel : +33 1 56 09 28 74 - Fax : +33 1 56 09 28 59
e-mail : Isabelle.heard@egp.aphp.fr

INTRODUCTION

Cervical intraepithelial neoplasia is the most important gynecological manifestation of HIV infection (Wright, 1994, Ellerbrock, 2000, Massad, 2001).
To increase our understanding of cervical disease in HIV-infected women, we initiated a prospective study in 1993 in two HIV out-patients clinics in Paris (Heard, 2000).
Although HAART has lowered the incidence of various opportunistic diseases (Mocroft, 2003), its impact on incidence of Cervical Intraepithelial Neoplasia (CIN) is unclear.
The purpose of the current study was to compare the incidence of CIN in HIV-infected women under HAART versus untreated HIV-positive women and to determine the role of risk factors in the pathogenesis of CIN.

PATIENTS AND METHODS

All women attending the gynecology outpatient clinic of the HIV departments of Hospital Pompidou and Hospitall Cochin, Paris, since June 1993 until May 2004 were offered to participate in a prospective gynecological survey. Eligibility criteria for enrollment in the study included documented HIV-positive status and consenting to the protocol. Among the 1041 eligible women, 1036 decided to enroll in the study, while five declined because of fear of loss of confidentiality by participating in a cohort of HIV-infected patients. The protocol was approved by the French National Agency for AIDS Research (ANRS).

The study included a structured questionnaire and gynecologic examination including a Papanicolaou smear and a standardized colposcopic examination of the cervix at enrollment and every six-months. At inclusion, normal smear and colposcopy were considered as no evidence of CIN.

Cervical cytology was employed as the sole endpoint. All smears were interpreted by the same pathologist (Dr C. Bergeron, Laboratoire Pasteur-Cerba, France) using the criteria of the Bethesda system. High-grade CIN were biopsy proven.

The most recent values of CD4+ cell counts and plasma HIV RNA within 6 months of the gynecologic examinations were obtained from clinical records.

HAART included at least two nucleosidic reverse transcriptase (RT) inhibitors in combination with either a protease inhibitor or a non-nucleosidic RT inhibitor or a third RT inhibitor. Women who were receiving fewer than 3 antiretroviral drugs were not considered to be on HAART.

Among the 1039 women enrolled in the cohort, 562 were diagnosed with CIN prior to or at enrollment. Of the 474 women with no history of CIN and normal cytology at enrollment, 316 had at least one follow-up visit. Fourty six among them presented with colposcopic abnormalities at initial examination and were thus excluded from the present study which is restricted to the 270 women with normal Pap smear and normal colposcopic findings at enrollment.

STATISTICAL ANALYSIS

- **A multiple Cox regression model** was used to identify risk factors for incidence of abnormal cytology.The end point of the present analysis was the detection by cytology of incident lesion. Follow-up was ended at the last visit for those who did not show lesions.
- Hormonal contraception, HAART and CD4 cell counts were included as time-dependent variables. The following factors were assessed: age, race, group of transmission, total number of sexual partners, hormonal contraception, condom use (consistent or no intercourse vs inconsistent or none), tobacco smoking, inclusion era (1993-94, 1995-96, 1997 onwards), HAART and CD4 cell count.
- Univariate analysis was used to screen for an association with incidence.

Variables with p<.20 were considered for inclusion in the final multivariate model in which the usual p <0.05 was considered as significant.

RESULTS

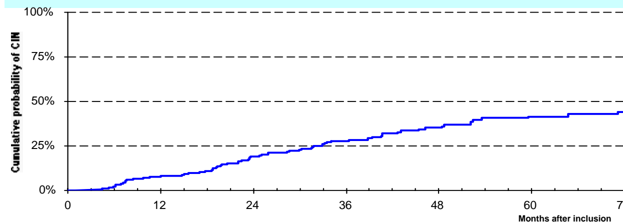
I-Characteristics of HIV-infected women at enrollment during three inclusion eras (n=270)

	1993-1994		1995-1996		?1997		Total		P
Women n (%)	91	(33.7)	95	(35.2)	84	(31.1)	270	(100.0)	
Age at inclusion									**0.02**
Median	31.3		33.8		34.2		33.2		
IQR [25-75]	[27.0 – 36.0]		[29.5 – 36.4]		[29.2 – 39.2]		[28.4 – 37.2]		
Ethnic origin									**0.13**
Caucasian n (%)	54	(60.0)	54	(58.7)	38	(45.2)	146	(54.9)	
Africa/Sub-Saharan n (%)	27	(30.0)	29	(31.5)	40	(47.6)	96	(36.1)	
Africa/Magreb, Other n (%)	9	(10.0)	9	(9.8)	6	(7.1)	24	(9.0)	
Missing n (%)							4		
Transmission group									**0.05**
Heterosexual contact n (%)	58	(68.2)	69	(78.4)	72	(85.7)	199	(77.4)	
IVDUs n (%)	23	(27.1)	17	(19.3)	8	(9.5)	48	(18.7)	
Blood contaminated n (%)	4	(4.7)	2	(2.3)	4	(4.8)	10	(3.9)	
Missing n (%)							13		
Tobacco smoking									**0.004**
Yes n (%)	41	(47.1)	42	(47.2)	21	(25.3)	104	(40.1)	
Missing n (%)							11		
Parity									**0.11**
?1 n (%)	57	(62.6)	50	(53.8)	19	(76.0)	126	(60.3)	
Missing n (%)							61		
Total number of sexual partners									**0.35**
?5 n (%)	51	(56.0)	48	(50.5)	48	(45.0)	135	(50.7)	
Missing n (%)							4		
Contraceptive pill use[1]									**0.02**
Yes n (%)	16	(17.6)	5	(5.3)	7	(8.3)	28	(10.4)	
Missing n (%)									
Condom use[1]									**0.04**
Consistent or no intercourse n (%)	51	(62.2)	68	(73.9)	67	(79.8)	186	(72.1)	
Missing n (%)									
CD4 group, cell /uL [1]									**0.10**
Median	424		375		432		400		
IQR [25-75]	[317 – 620]		[240 – 515]		[280 – 650]		[280 – 595]		
Missing	5		8		5		18		
HIV-RNA copies/ml [1]									**0.06**
Median			10000		320		499		
IQR [25-75]			[701-38955]		[50-4945]		[50-9908]		
Missing	91		83		9		183		

[1] Contraceptive pill use , Condom use, CD4 and HIV-RNA at inclusion

Women differed for transmission group, tobacco smoking, hormonal contraception and condom use in the various inclusion eras.

II- Kaplan-Meier estimates for the cumulative probability of CIN



During a median follow-up of 28 months, (867 patients-years), incident CIN was identified in 83 women (**incidence of 9.6 cases per 100 person-years**). Of CIN, 70 were low-grade. No invasive cervical cancer was identified.
The cumulative incidence of CIN was estimated to be 8% at one year and 19% at two years.

III-Univariate and multivariate analysis of factors associated with risk for cervical intraepithelial lesions during follow-up (n=270)

			Cox Model					
		CIN	Univariate			Multivariate		
	N	Rates at 2 years[1]	RR	[95% CI]	P	RR	[95% CI]	p
Age at inclusion								
? 40	44	4.9	1			1		
30 - 39	139	24.9	3.4	[1.5 8.0]		3.1	[1.2 8.1]	
19 - 29	87	16.5	2.3	[1.0 5.7]	**0.009**	2.3	[0.8 6.4]	**0.05**
Ethnic origin								
Caucasian	146	20.7	1			1		
Africa/Sub-Saharan	96	13.4	0.7	[0.4 1.1]		0.6	[0.3 1.1]	
Africa/Magreb, Other	24	20.9	1.2	[0.6 2.4]	**0.17**	1.1	[0.5 2.2]	**0.24**
Transmission group								
Heterosexual contact	199	20.9	1					
IVDUs	48	16.6	1.1	[0.6 1.8]				
Blood contaminated	10	0	0.0		**0.97**			
Tobacco smoking								
No	155	14.1	1			1		
Yes	104	21.9	1.9	[1.2 2.9]	**0.008**	1.1	[0.6 1.9]	**0.80**
Parity								
0	83	21.0	1					
?1	126	19.7	0.9	[0.5 1.4]	**0.56**			
Total number of sexual partners								
<5	131	12.6	1			1		
?5	135	24.0	1.7	[1.1 2.7]	**0.02**	1.3	[0.8 2.3]	**0.28**
Contraceptive pill use[2]								
No	242	16.4	1			1		
Yes	28	31.8	2.1	[1.2 3.7]	**0.009**	1.7	[0.9 3.2]	**0.13**
Condom use[2]								
Inconsistent or none			1			1		
Consistent or no intercourse			0.6	[0.3 0.9]	**0.01**	0.9	[0.5 1.6]	**0.80**
CD4 group, cell /uL [2]								
?500			1					
200-500			1.1	[0.7 1.7]				
<200			1.3	[0.7 2.5]	**0.73**			
Inclusion era								
1993-1994	91	9.3	1			1		
1995-1996	95	35.5	2.2	[1.3 3.5]		2.2	[1.3 3.8]	
? 1997	84	10.2	0.9	[0.4 1.8]	**0.001**	1.4	[0.7 3.1]	**0.02**
HAART use[2]								
No			1			1		
Yes			0.6	[0.3 0.9]	**0.02**	0.5	[0.3 0.9]	**0.02**

[1] Kaplan-Meier rates.
[2] included as time-dependent variables at time of visit.

By multivariate analysis, significant risk factors for incident CIN were:
Age 30-39 : hazard ratio (HR) 3.1 (95%CI, 1.2-8.1),
with ≥40 years taken as reference.

Women enrolled in 1995-96 : HR= 2.2 (95%CI, 1.3-3.8),
with 1993-1994 taken as reference.

Women under HAART
HR=0.5 (95%CI, 0.3-0.9)
Incidence decreased from **11.8 to 6.8** per 100 person-years in non treated versus treated women.

Conclusions

1. In our study, 1 in 5 HIV-infected women with no evidence of cervical lesion developed squamous intraepithelial lesions within 2 years.
2. Women differed for factors that may modulate the risk for development of CIN in the different inclusion eras.
3. Of incident CIN, 84% were low-grade, and no invasive carcinoma were identified during 867 patient-years of follow-up.
4. The association of CD4 cell counts with incident CIN was not significant.
5. Women under HAART exhibited a two fold decrease in risk to develop CIN during follow-up.

Acknowledgments

This work was supported by:The French National Agency for AIDS Research
The cooperation of the women who have participated in the prospective gynecological study initiated in 1993 in the HIV departments of Hospital Pompidou and Hospital Cochin, Paris, France.