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Marie-Pierre Drogoul-Vey, Catherine Marimoutou, Andrée Robaglia-Schlupp, Mouna Beerli, Jean-Albert Gastaut, et al.. Determinants and evolution of Squamous Intraepithelial Lesions in HIV-infected women, 1991-2004. AIDS Care, 2007, 19 (08), pp.1052-1057. 10.1080/09540120701295242 . hal-00513423

HAL Id: hal-00513423 https://hal.science/hal-00513423

Submitted on 1 Sep 2010

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Journal:	AIDS Care - Psychology, Health & Medicine - Vulnerable Children and Youth Studies
Manuscript ID:	AC-2006-09-0144
Journal Selection:	AIDS Care
Keywords:	HIV infection , Pap smear, Squamous Intraepithelial Lesion, cervix cancer, HAART



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Short Title: Determinants of SIL in HIV-infected women

Full text: 2512 words, 2 tables Summary: 217 words

Abstract

This study present a Case-control nested analysis of cervical squamous intraepithelial lesions (SIL) in a cohort of 423 HIV-infected women with registered Pap smears between 1991 and 2004. Data on Pap smear results, CDC HIV classification, CD4 cell count and antiretroviral therapy were prospectively collected. Pap smears were classified using the Bethesda classification. Women had a median of 3 Pap smears registered in the database. The first Pap smear was registered ≤1996 for 57.7%. Two hundred and twenty women were diagnosed with SIL at least once, mainly at their first screening. Compared to women free of SIL and cancer at all Pap-smear, they were younger, had lower CD4 cell count and were more likely included ≤1996 and less likely treated with HAART. These differences persisted in multivariate analysis. Among the 142 women with secondary pap smears after SIL diagnosis, 43 (30.3%) worsen their Pap smear results. No specific characteristics could be identified for these patients compared to those who did not. Finally 21 women were diagnosed with cervix cancer, 3 at first Pap smear and the others after a previous SIL diagnosis in a median delay of 3 years. These results reflect the change in gynecologic management of HIV-infected women after HAART introduction but also underline the necessity to maintain a regular gynecologic screening for HIV-infected women.

Key words: HIV infection, Pap smear, SIL, cervix cancer, HAART

Introduction

HIV-infected women have been described as being at higher risk for squamous intraepithelial lesions (SIL) and cervix cancer since the beginning of the HIV epidemic. This led to the inclusion of cervix cancer in AIDS diseases in the 1992 CDC revised classification. Since that time, gynecologic screening including Pap smears has been strongly recommended as a part of the regular follow-up of HIV-infected women {Delfraissy JF, 2004 #24}.

Previous studies have reported the incidence of SIL as between 8.9 and 11.5/100 person-years (Massad LS, Ahdieh L et al. 2001; Schuman P, Ohmit SE et al. 2003). Different factors have been reported to be associated with SIL occurrence, principally the existence of Papilloma virus (HPV) infection (Cardillo M, Hagan R et al. 2001; Massad LS, Ahdieh L et al. 2001; Hawes SE, Critchlow CW et al. 2003; Schuman P, Ohmit SE et al. 2003; Heard I, Palefsky JM et al. 2004; Harris TG, Burck RD et al. 2005; Lillo FB, Lodini S et al. 2005) and immunosuppression (Cardillo M, Hagan R et al. 2001; Schuman P, Ohmit SE et al. 2003; Heard I, Palefsky JM et al. 2004; Taylor G, Wolff T et al. 2004; Harris TG, Burck RD et al. 2005). The role of highly active antiretroviral therapy (HAART) is still debated – some studies have reported a lower incidence of SIL after 1996 but the direct influence of HAART on incidence of SIL is not well defined (Heard I, Palefsky JM et al. 2004).

The aim of this study was to describe cervical Pap smear results in HIV-infected women followed up since 1991 and to compare women diagnosed with SIL to others in regard of previously identified risk factors (age, mode of contamination, CD4 cell count, antiretroviral treatment).

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Materials and Methods

Prospective observational cohort of gynecologic follow-up of HIV infected women referred to a single HIV-specialized hospital care unit, the CISIH-Sud of Marseille, France. Since 1991, this hospital unit has proposed to HIV-infected women a gynecologic consultation with a specialist who systematically performed a screening of cervical squamous intraepithelial lesions (SIL) using conventional Pap smears. The results of Pap smears, demographic data, HIV therapy and CD4 cell count were prospectively collected for women who gave their informed consent.

All of the Pap smears were collected using a endocervical cytological brush. The specimens were smeared onto one or two slides, fixed immediately, and then sent to the same laboratory. After technical preparation and Papanicolaou staining, each Pap smear was first examined by a cytotechnologist and then evaluated by the same cytopathologist all through the study period. Pap-smear results were classified using the Bethesda classification (Kurman RJ, Malkasian GD Jr et al. 1991)according to the 2001 consensus guidelines (Wright TC, Cox JT et al. 2002), without subdividing the atypical squamous cells (ASC) into 2 categories because our cohort was set up fifteen years ago and the first Pap smears could not be reclassified.

In this database of women with Pap smear results we performed a case-control nested study, comparing women presenting at least once a diagnosis of SIL with those free of SIL at all registered Pap smears. They were compared according to their characteristics at first Pap smears performance (i.e. inclusion in the database) and at the time of diagnostic of SIL for those with SIL or last Pap smear results for others. The associations between age, contamination route, year of first pap-smear performance, CDC stage classification of HIV infection, CD4 cell count, antiretroviral treatment and SIL were evaluated using Chi² or Kruskall-Wallis tests and logistic regression. Statistical analyses were performed by STATA[™].

Results

The data for 423 women screened for cervical SIL between September 1991 and June 2004 were collected. The patients were predominantly contaminated through heterosexual intercourse (48.5%) and intravenous drug use (IDU, 41.1%). When the first Pap smear was performed (baseline), the median age was 33 years (range: 17 to 75 years) with a median exposure to HIV for 5 years. Their median CD4 cell count was 341 cells/mm³, 56.5% were antiretroviral treated, 16.1% receiving monotherapy, 14.9% bitherapy and 25.5% tritherapy or more (HAART) (Table 1). Antiretroviral treatment exposure differed according to the time period of first Pap-smear performance, 35.7% of patients were treated before 1995, 48.2% in 1995-1996, and 79.3% after 1996. For the 239 patients who were treated, median antiretroviral exposure was 1.2 years in the first two periods but 3 years in the post-1996 period. Furthermore, the proportion of treated patients increased during follow-up.

Characteristics of patients with or without SIL

Among the 423 women who entered the database, 139 (33%) had Pap smear examination only once. Globally, the median number of Pap smears by women was 3 [IQ: 1-6]. In order to increase the power of analysis, the whole sample of Pap smears was considered to identify patients with SIL. Two hundred and twenty women (52%) presented SIL at least once in the database. The first SIL was considered for this analysis. It was diagnosed at the first Pap smear performance in 154 (70%) women and later during follow-up (median delay of occurrence 25 months; Interquartile: 9-41 months) in 66 (30%). The SIL was classified low grade for 64.5% and high grade for 35.5%. Three patients were diagnosed with cervix cancer at first Pap smear and were excluded of the comparison. The 200 women free of SIL at all Pap smears examinations were 96 (48%) seen only once and for the 104 others had their last Pap smear in a median delay of 28 months [11-60 months]. Characteristics of these patients

according to the diagnosis of SIL are summarized Table 2. The 220 patients with SIL were more likely contaminated through intravenous drug use. They were younger, examined for the first time sooner (72.3% were first examined \leq 1996 compared to 43.0% in the non SIL group), had a lower CD4 cell count and were antiretroviral treated in about the same proportion but more frequently with mono or bitherapy. Those differences were significant as well when comparing baseline or last characteristics (i.e. at the time of SIL or at the last Pap smear for patients without SIL). It is to be noted that most of patients characteristics were considered only at baseline whether patients presented SIL at this time (70% of the SIL group) or they were seen only once (48% of the non SIL group). However, considering the follow-up characteristics increased the differences (Table 2).

The multivariate logistic regression including characteristics at the time of SIL finally found a higher risk of SIL when patients were younger (OR=0.95, CI=0.92-0.98 for one year younger), examined for the first time \leq 1996 (OR: 1.88, CI: 1.12-3.22), had a lower CD4 cell count (OR: 0.98; CI: 0.97-0.99, for each decrease of 10 cells/mm³). Adjusted on all these parameters and compared to no treatment, treatment with HAART tended to be protective for SIL diagnostic (OR: 0.57; CI: 0.31-1.04, p=0.065). No difference was observe for mono or bitherapy. The association between contamination by IDU and SIL diagnosis was no longer significant.

In regard of follow-up data, the median delay between first and second Pap-smear examination was 10.5 months [IQ: 6-18 months]. It did not differ between women with or without SIL neither between those seen first \leq 1996 or after.

SIL evolution

Among the 220 women with SIL, 142 had follow-up data after first SIL (65.5% low grade and 34.5% high grade). They were 30.3% (n=43) to present a worsen SIL during follow-up

in a median delay of 27 months (IQ: 11-46 months), 33.3% among the low grade SIL and 24.5% among the high grade (p=0.28). Among the 31 low grade SIL, 27 reached high grade and 4 cancer. Moreover, 12 high grade SIL were diagnosed cancer during follow-up. Consequently 16 patients (11.3% of patients with SIL and further examination) presented cervix cancer during follow-up in a median delay of 32 months (IQ: 23-66 months). The median duration between SIL diagnosis and last Pap smear for patients who did not aggravate their Pap smear classification was 45 months (IQ: 18-80 months).

The patients who worsen their SIL did not differed of others in regards of their characteristics at the time of first SIL or their year of first Pap smear examination, although their median CD4 cell count tended to be lower 274 [103-432] versus 344 [196-483], p=0.13. However, at the time of diagnosis of the worsen SIL, the CD4 cell count distribution did not significantly differed (median 268; IQ: 180-425) and the median delta of CD4 was –25 cells/mm³ [IQ: - 114;+36]. Finally, patients with worsen SIL had had 3 Pap smears [IQ: 2-5] recorded in median between the first SIL and the worsen SIL versus 4 Pap smears [IQ: 3-7] for those with no worsen SIL.

Cancer of the cervix

In the whole sample of patients, 21 (5.0%) were diagnosed once with cervix cancer, three at first examination and 18 during follow-up, most of them after a previous diagnosis of low or high-grade SIL. Majority (13/21) of these women has been included in the database \leq 1996, but only 5 cancer were diagnosed at this period. At inclusion, they were 7/21 classified CDC stage C, 62% were contaminated with UDI (n=13), their median CD4 cell count was 315/mm3 (range: 15-1259). At this time only 3 patients received tritherapy, 4 bitherapy, 6 monotherapy of nucleoside analogues and 8/21 were not treated.

The median delay between first Pap examination and cancer diagnosis was 37 months. Unless for the 3 patients diagnosed at first Pap smear, the range distribution of this delay was 4 to 139 months. At the time of cancer diagnosis, women were median aged of 35 years (range: 26-64 years), 25% had a CD4 cell count <200/mm3, 7/21 were at AIDS stage. The great majority (19/21) were ARV treated, 10/21 receiving at least tritherapy and only 2 a monotherapy. Patients diagnosed with cancer had had 4 Pap smears examination in median. Finally, 18 cervix cancers were diagnosed in the 267 women with follow-up data (median follow-up of 4 years), representing a incidence of cancer of 1.2 per 100 persons-years of follow-up.

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Discussion

In this historic study, the prevalence of SIL was high, more than a half of women presenting SIL at least once, and diagnosis of SIL was predominantly performed at first Pap smear examination. The case control analysis confirms the pejorative role of immuno-suppression on SIL risk. Women with SIL were also younger and more likely included before 1996. However, even adjusted on theses factors HAART tended be protective of SIL diagnosis. Moreover, unless patients were somehow regularly screened with Pap smears, Pap smear classification aggravated in 30% of patients with SIL and conducted to cancer in 11%.

This study corresponds to data collected under routine conditions in women followed up in an HIV-specialized unit. However, gynecologic screening was not systematically accepted by the women, who could choose to be followed up by a gynecologist out of the unit or not followed up at all. A selection bias cannot be denied. Nevertheless, the repartition of contamination mode, age and antiretroviral treatment in this sample is similar to that of the whole population of women followed up in the unit.

The association between low CD4 cell count and SIL has largely been reported in literature (Cardillo M, Hagan R et al. 2001; Massad LS, Ahdieh L et al. 2001; Hawes SE, Critchlow CW et al. 2003; Schuman P, Ohmit SE et al. 2003; Taylor G, Wolff T et al. 2004; Harris TG, Burck RD et al. 2005), although the significant threshold may differ. For Harris *et al.*, there was no difference in the two-year incidence of SIL between HIV-infected women over 500 CD4/mm³ and seronegative women, the incidence rose when the CD4 cell count declined <500/mm³ (Harris TG, Burck RD et al. 2005). However, Massad *et al.* found that the significant cut-off was 200 CD4 mm³ (Massad LS, Ahdieh L et al. 2001). In our study we considered CD4 cell count as a continuous variable, if converted in dummy-variable in three

threshold (CD4<200, between 200-499 and >500), both threshold <200 and <500 were significant on the risk of SIL (data not shawn).

In our study, younger women were at higher risk of developing SIL, suggesting either lower protection against infection due to younger age or more risky behavior for HPV infection. In recent studies focusing on the effects of HAART, age was not reported as a risk factor for SIL (Schuman P, Ohmit SE et al. 2003; Ahdieh-Grant L, Li R et al. 2004; Heard I, Palefsky JM et al. 2004; Taylor G, Wolff T et al. 2004). However, patients with cervix cancer were older, suggesting the necessity of longer duration of either HPV or HIV infection.

Patients contaminated though IDU are suspected of being at more at-risk behavior in terms of sexual activity or addiction to tobacco. We did not recorded such behavioral data but no difference between women infected with IDU and others was observed in multivariate analysis. Moreover, Schumann *et al.* in the HER study did not find any association between SIL and tobacco use or sexual activity (Schuman P, Ohmit SE et al. 2003).

In the literature, a slight effect of HAART on SIL occurrence or regression has been reported (Ahdieh-Grant L, Li R et al. 2004; Heard I, Palefsky JM et al. 2004; Taylor G, Wolff T et al. 2004), but it appeared to be mediated by a CD4 increase (Ahdieh-Grant L, Li R et al. 2004). Our results concluded to a trend in favor of a protective role of HAART compared to no treatment after adjustment on CD4 cell count and year of inclusion. However, HPV is known to interfere with SIL and HAART has no direct effect of on HPV infection (Heard I, Palefsky JM et al. 2004). This trend should eventually be confirmed on larger sample with HPV infection recorded. In this study, HPV coinfection was not tested in all of the patients since the study began before HPV detection was routinely performed. However, French guidelines for HIV infection care do not recommend HPV testing but a systematic annual Pap smear if CD4>200/mm³ and twice a year in case of CD4<200/mm³ {Delfraissy JF, 2004 #24}.

The main result of this study is that unless for cancer occurring on previously observed abnormal cervix, most of abnormalities were detected at the first Pap smear performance. This was particularly true when considering the oldest data (i.e. first Pap \leq 1996). These patients were less antiretroviral treated or if so with less effective therapy. Moreover, they had a lower CD4 cell count at the first Pap smear. So, it can be concluded that evolution of care after HAART introduction more likely than direct effect of HAART had a major impact on SIL risk in HIV infected patients. However, even with antiretroviral treatment, we observed an aggravation of SIL classification in 30% of women. A previous study by Delmas *et al.* associating data of 20 women of this cohort showed that 8% of the women with CIN1 had progressed to high-grade lesions at one year (Delmas MC, Larsen C et al. 2000) and Massad *et al* observed 14% aggravation of abnormal smears (including ASCUS) at six months(Massad LS, Ahdieh L et al. 2001). In this study no determinant significantly differed women who progressed from those who did not. No specific role of CD4 cell count was also observed in Massad *et al* study after adjustment of HPV status (Massad LS, Ahdieh L et al. 2001).

We also found women diagnosed with SIL at risk of progression to cervix cancer suggesting a lack of either SIL management or efficiency of treatment in this population. The delay between first and second Pap smear did not differ between patients with or without SIL, favoring the hypothesis of problems in curative therapy options in these patients. The high frequency of SIL recurrence is well known in this population even when HAART treated and has been reported elsewhere(Gilles C, Manigart Y et al. 2005). Finally, the incidence of cancer was high in our study compared to results observed in US-HIV-infected women included in a prevention program(Massad LS, Seaberg EC et al. 2004). This result seem coherent with the observation of increase of cervix cancer between the 1993-1996 and 1997-1998 periods by Italians(Franceschi S, Dal Maso L et al. 2003) and the results of the Swiss

cohort which find this type of cancer persistently 8-fold higher than in seronegative women with no influence of HAART (Clifford GM, Polesel J et al. 2005).

In conclusion, our results reflect change in women care after the introduction of HAART but also stress the necessity to maintain a regular gynecologic screening in HIV-infected women. The role of specific gynecologic treatment on secondary cancer in HAART-treated patients with SIL should be studied prospectively.



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	Total	
	N=423 (%)	
Contamination route		
Heterosexuality	205 (48.5)	
Intravenous drug use	174 (41.1)	
Blood receipt	12 (2.8)	
Unknown	32 (7.6)	
Median age in years	32.8	
[Interquartile range]	[28.4-37.5]	
Year of inclusion	158 (37.4)	
<1995	86 (20.3)	
1995-1996	179 (42.3)	
≥ 1996		
Exposure to HIV infection (years)	5.4 [2.1-8.0]	
CDC classification		
stage A	184 (43.5)	
stage B	141 (33.3)	
stage C	98 (23.2)	
Median CD4 cell count/mm ³	341	
[interquartile range] N=404	[180-494]	
<200 CD4/mm ³	106 (26.2)	
Antiretroviral treated	239 (56.5)	
Monotherapy (all NRTI)	68 (28.5)	
Bitherapy (59 with 2 NRTI [94%])	63 (26.4)	
Tritherapy (43 [63%] with 2NRTI+1PI; 20 [29%]	92 (38.5)	
2NRTI+1NNRTI; 24 [35%] 3 NRTI)	16 (6.7)	
Quadritherapy (11 [69%] with 2 NRTI+2 PI)		
Antiretroviral treatment duration in years $(n=194)$	2.7[0.7-5.7]	
Initial Pap smear results		
Normal	156 (36.9)	
ASCUS	111 (26.3)	
Low grade SIL	97 (22.9)	
High grade SIL	56 (13.2)	
Cervix cancer	3 (0.7)	

Table 1: Baseline characteristics of women at the time of first Pap smear, n=423

	Patients with SIL N=220	Patients without SIL N=200	р			
Contamination by IDU	99 (45.0%)	71 (35.5%)	0.05			
CDC classification						
Stage A	72 (32.7)	111 (55.5)	<0.0001*			
Stage B	89 (40.5)	50 (25.0)				
Stage C	59 (26.8)	39 (19.5)				
Year of first examination	1995 [1993-1997]	1997 [1994-2000]	0.0001			
Baseline Characteristics						
Age in years Median (IQR)	32 [27-35]	35 [30-40]	0.0001			
CD4 cell count	313 [153-457]	383 [262-549]	0.0001			
Median (IQR)						
Antiretroviral therapy			0.0001			
None	104 (47.3)	81 (40.5)	<0.0001			
Monotherapy	48 (21.8)	20 (10.0)				
Bitherapy	27 (12.3)	35 (17.5)				
HAAKI	41 (18.6)	64 (32.0)				
Characteristics at SIL diagnosis or last Pap smear free of SIL						
Age in years						
Median (IQR)	32 [28-36]	36 [32-43]	0.0001			
CDC classification						
Stage A	70 (31.8)	111 (55.5)	<0.0001**			
Stage B	87 (39.5)	50 (25.0)				
Stage C	63 (28.6)	39 (19.5)				
CD4 cell count †	313 [156-433]	393 [259-557]	0.0001			
Median (IQR)						
Antiretroviral therapy	04 (42.7)	50 (20 5)	.0.0001			
INONE	94 (42.7)	59 (29.5) 15 (7.5)	<0.0001			
wonotnerapy	41(18.0)	15 (7.5)				
ounerapy	30 (10.4) 40 (22.2)	40(20.0)				
ΠΑΑΚΙ	49 (22.3)	80 (43%)				

Table 2: Characteristics of patients according to SIL diagnosis, N=420

IDU: intravenous drug use; IQR: interquartile range

* Proportion of stage C tended to be significantly higher in the SIL group (p=0.08)

** Proportion of stage C was significantly higher in the SIL group (p=0.04)

[†] For patients whose data were not inclusion data (n=66 in the SIL group and 104 in the non SIL group) the CD4 cell gain was +2 [-84;130] for the non SIL group and -18 [-84;+130] in the SIL group, p=0.20.