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Evolution of Cervical Cytologic Changes among HIV-Infected Women with Normal Cytology in the HAART Era

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ABSTRACT

The influence of HAART on the evolution to cervical squamous intraepithelial lesions (SIL) among HIV$^+$ women with a normal cytological test in the HAART era was studied. A retrospective cohort study (1997–2005) of HIV-infected women treated with HAART was conducted. Those with a normal cervical cytology (Papanicolaou test) and at least one subsequent test were included. Survival (time until diagnosis of SIL), univariate, and multivariate analyses were performed. A total of 133 HIV-infected patients treated with HAART were included. The incidence of SIL was 35% (47 patients). SIL was diagnosed in 36 of 110 (33%) patients with a baseline and final immunological status of >200 CD4 cells/μl and in 6 of 9 (67%) patients with a baseline and final immunological status of ≤200 CD4 (OR: 0.24, 95% CI: 0.06–1.03, $p = 0.041$). SIL was diagnosed in 10 of 60 (17%) patients with an undetectable baseline and final HIV viral load and in 36 of 70 (51%) patients with a detectable HIV viral load (OR: 0.19, 95% CI: 0.07–0.46, $p < 0.001$). A high incidence of SIL (cancer precursor lesions) was observed among HIV$^+$ women without a background of cervical pathology. The effect of HAART on the control of HIV replication and of immunological status (>200 CD4) through the follow-up was associated with a reduction of SIL.

INTRODUCTION

CERVICAL SQUAMOUS INTRAEPITHELIAL LESIONS (SIL) are precursors to invasive cervical cancer, which has been shown to be related to human papillomavirus (HPV) infection.[1,2] HIV infection may increase the risk of HPV infection, promote the reactivation of a latent infection, or permit infection persistence. Indeed, HPV infection is more prevalent and persistent in HIV$^+$ women, which thereby contributes to a higher risk for invasive cervical cancer and its precursor lesions. Likewise, some data have suggested that about 20% of HIV$^+$ women without evidence of cervical disease will develop SIL within 3 years.[3–5]

Highly active antiretroviral therapy (HAART) controls HIV replication and improves immunological status by increasing CD4 cell counts. Theoretically, this immune restoration could reduce the risk of cervical SIL, delaying or normalizing the evolution of cervical cytological changes. However, HAART also prolongs life expectancy; this might increase the probability of HPV exposure and the accumulation of genetic somatic mutations, thereby increasing the probability of developing cervical disease. But these possibilities have not yet been confirmed. Limited and contradictory data are available on the evolution of cervical cytological changes in HIV$^+$ women treated with HAART,[6–15] and the role of HAART in the incidence of cervical SIL among HIV$^+$ women without cervical HPV-related pathology is not well established.

On the other hand, cervical cytology is undoubtedly the most suitable diagnostic technique and has contributed dramatically to the reduction in mortality related to cervical cancer. Atypical squamous cells of undetermined significance (ASCUS), the most common abnormal finding of cervical cytological testing, is an outcome with an uncertain meaning that even expert cy-

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topathologists are unable to classify as reactive alterations or as premalignant lesions.[16,17] The etiology and the outcomes of ASCUS are uncertain, as the name implies, and limited data on ASCUS are available.[18,19]

Therefore, the objective of this retrospective study was to generate data about the long-term effect of HAART on the incidence of cervical SIL among HIV^+ women with a normal baseline cytological test and without a previous history of cervical pathology, as well as to generate data about the evolution of lesions (regression or progression) in patients who were diagnosed with ASCUS.

MATERIALS AND METHODS

Between January 1997 and December 2005, all patients included in the database of the HIV Clinical Unit of the Germans Trias i Pujol University Hospital were evaluated. HAART therapy became widely available in our hospital at the beginning of 1997, so this was considered the starting point of the study.

The patients eligible for the study had to fulfill the following inclusion criteria: women with an HIV^+ diagnosis and two consecutive normal cervical cytological tests [Papanicolaou (Pap) test] and at least one subsequent test and women who were treated with HAART between cytologies were included in the study. The exclusion criteria included having a previous history of cervical dysplasia or a cancer diagnosis.

The following data were also gathered at baseline: date of birth, date of cervical cytologies, date of HIV^+ diagnosis, CD4 cell count ($\pm$1 month from the date of a normal Pap test), CD4 nadir previous to inclusion, HIV viral load (HIV_VL) ($\pm$1 month from the date of a normal Pap test), HAART previous to inclusion, number of sexual partners, number of patients with a history of pregnancies and other risk factors such as intravenous drug abuse, and a history of smoking. Likewise, the following data were gathered between cytologies: CD4 nadir, CD4 cell count ($\pm$1 month from the date of Pap test), HIV_VL ($\pm$1 month from the date of Pap test), and information on the patients' treatment with HAART, which was strictly checked. HAART included at least two nucleoside reverse transcriptase inhibitors in combination with either a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor.

Study design

This was a retrospective cohort study, based on the cohort of outpatient women treated by the gynecologists (A.T., N.G.) of the HIV Unit of a university tertiary hospital.

Cervical cytology

The Pap test was the standard diagnostic technique used routinely in gynecological examination. The cytological changes were classified according to the Bethesda System[16]: normal, no cell changes; ASCUS, atypical squamous cells of unknown significance; LSIL, low-grade squamous intraepithelial lesions; and HSIL, high-grade squamous intraepithelial lesions. Usually, all samples were checked by two cytopathologists (M.L., E.C.). Generally, when a patient is diagnosed with a squamous intraepithelial lesion (low or high), a colposcopy and biopsy are proposed in order to verify the cytological result and to proceed to conization if the biopsy confirms an HSIL or carcinoma.

Due to the fact that ASCUS is an outcome with an uncertain meaning and is difficult to classify (even by expert cytopathologists), and in order to avoid possible background noise, it was analyzed independently.

Influence of HAART effect on immunological status (CD4) and on HIV viral load, and its impact on the evolution from a normal cervical cytological test to SIL

To study the impact of HAART on the evolution from a normal cervical cytological test to SIL, the patients were divided according to the value of baseline and final CD4 lymphocyte count (200 and 350 cells/μl) and according to the value of baseline and final HIV_VL (undetectable $\leq$50 copies).

The following requirements were considered to perform the survival analysis, time until SIL. The baseline moment was the date of the normal cytology test. When a cervical cytology of SIL (or carcinoma) was diagnosed, the date of this Pap test was used for survival analysis (time until SIL). This information had to be confirmed with a subsequent positive result from the histology (biopsy), or if it was not available, with a second positive Pap test result. If the patient did not present any change, that is, if the patient presented several successive normal Pap test results, the date of the last test available in the database was considered for survival analysis (censored time).

Influence of HAART on the evolution from an ASCUS diagnosis to a normal cervical cytological test (regression) or to SIL or carcinoma (progression)

This second study was focused on establishing data about the evolution o ASCUS, thereby providing information about the significance of ASCUS cytology in HIV-positive women. The following requirements were followed to study the evolution of an ASCUS diagnostic. All women included in the previous analysis who were diagnosed with ASCUS and with at least one subsequent Pap test result were considered for this one. If the patient did not present any change, that is, if the patient remained with successive ASCUS Pap test results, the date of the last test available in the database was considered for the analysis. If the patient presented a normal Pap test result after the ASCUS diagnostic, another Pap test was necessary in order to verify this result. If the Pap test showed an SIL (or carcinoma), the result had to be confirmed with a subsequent positive result from the histology (biopsy), or if it was not available, with a second positive Pap test result.

Statistical analysis

A descriptive analysis was performed by baseline population. Continuous data are summarized as mean $\pm$ standard deviation (minimum; maximum).

The evolution of cervical cytology (SIL incidence during follow-up) was studied with Kaplan–Meier curves and the differences were assessed with the Mantel–Haenzel log-rank test, the Breslow test, and the Tarone–Ware test. Univariate analysis and multivariate proportional hazards regression (Cox regression) were performed to determine which of the following factors

Table 1. Baseline Characteristics of the Population Included in the Study[a]

Baseline characteristics	n = *133*
Age (years) (mean ± SD)	34.8 ± 8.7
Older than 40 years old [*n* (%)]	15 (11.3%)
HIV-1 RNA load (copies/ml) (mean ± SD)	6776 ± 31617
CD4 cell count cells/μl (mean ± SD)	502 ± 295
≤200 cells/μl [*n* %)]	20 (15.0%)
>200 and ≤350 cells/μl [*n* %)]	23 (17.3%)
>350 and ≤500 cells/μl [*n* %)]	30 (22.6%)
>500 cells/μl [*n* %)]	60 (45.1%)
HAART previous to inclusion	47 (35.3%)
Time of known HIV infection (years)	6.0 ± 3.9
Number of partners (mean ± SD)	12.8 ± 40.5
Patients with history of pregnancies [*n* %)]	60 (45.1%)

[a]Patients with normal cervical cytology (Papanicolaou test) and without previous history of cervical pathology.

would predict SIL: age, age of cervical cytology, time of HIV diagnosis, baseline CD4, CD4 nadir (previous inclusion and between cytologies), HIV_VL, HAART previous inclusion, number of partners, history of pregnancies, and other risk factors such as intravenous drug abuse and tobacco use. Odds ratios (OR) and Hazards ratios (HR) comparing SIL diagnosis and their corresponding 95% confidence intervals (95% CI) were estimated. A p value of ≤0.05 was considered statistically significant.

All data were recorded in a database program (Microsoft Access for Windows XP, Redmont, CA). Data analysis was performed using the statistical software programs SPSS for Windows version 12.0 (Apache Software Foundation, SPSS Inc., Chicago, IL) and StaXact (version 7; Cytel Inc., Cambrigde, MA).

RESULTS

Patient characteristics

One hundred and thirty-three patients, who met the inclusion and exclusion criteria, were included in the study during the period between January 1997 and December 2005. Baseline patient characteristics are summarized in Table 1. The average time to SIL development was 902 ± 689 days (min: 65; max: 2808). The average number of visits between baseline and final cytologies was 4.6 ± 3.1 (min: 2; max: 18). SIL was diagnosed in 47 of 133 (35%) patients. Figure 1 shows the actuarial probability (Kaplan–Maier curve) of remaining free of SIL.

Effect of HAART on immunological status (CD4) and its impact on the cervical cytological evolution

SIL was diagnosed in 6 of 9 (67%) patients with a baseline and final immunological status of ≤200 CD4 cells/μl, in 5 of 11 (46%) with ≤200 CD4 at baseline and >200 CD4 at the final analysis, and 36 of 110 (33%) with a baseline and final immunological status of >200 CD4. Three patients with >200 CD4 at baseline and ≤200 CD4 at the final analysis did not develop SIL. Therefore, the percentage of patients developing SIL varied according to immunological status. Figure 2A shows the actuarial probability (Kaplan–Maier curve) of remaining free of SIL in the groups of patients stratified by immunological status (200 CD4) between cytologies (log rank, $p = 0.012$; Breslow, $p = 0.014$, Tarone–Ware, $p = 0.012$). Univariate analysis showed that undetectable baseline HIV_VL (OR: 0.13, 95% CI: 0.06–0.31, $p < 0.001$) and baseline CD4 cell count were independent predictive factors for remaining free of SIL. Table 2 shows the number and percentages of patient diagnoses of SIL during the complete follow-up period grouped by baseline CD4 lymphocyte count (cells/μl). The actuarial probability of remaining free of SIL in the groups of patients stratified by baseline CD4 lymphocyte count of 350 cells was 53% in the group of ≤350 CD4 baseline group and 70% in the >350 CD4 base-

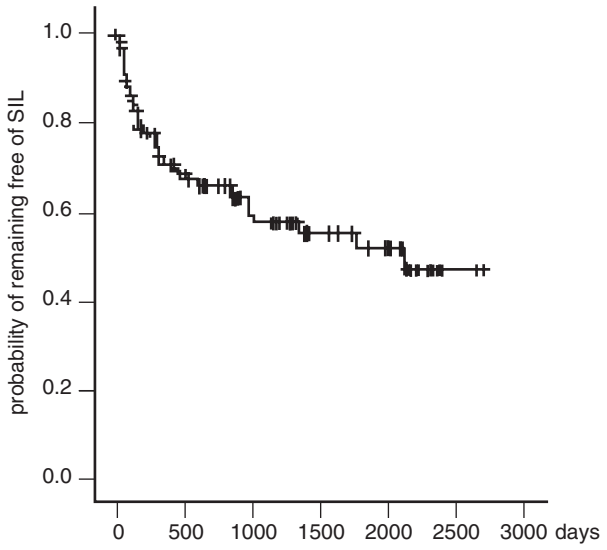

FIG. 1. The actuarial probability (Kaplan–Meier curve) of remaining free of SIL in patients with normal baseline cervical cytology ($n = 133$).

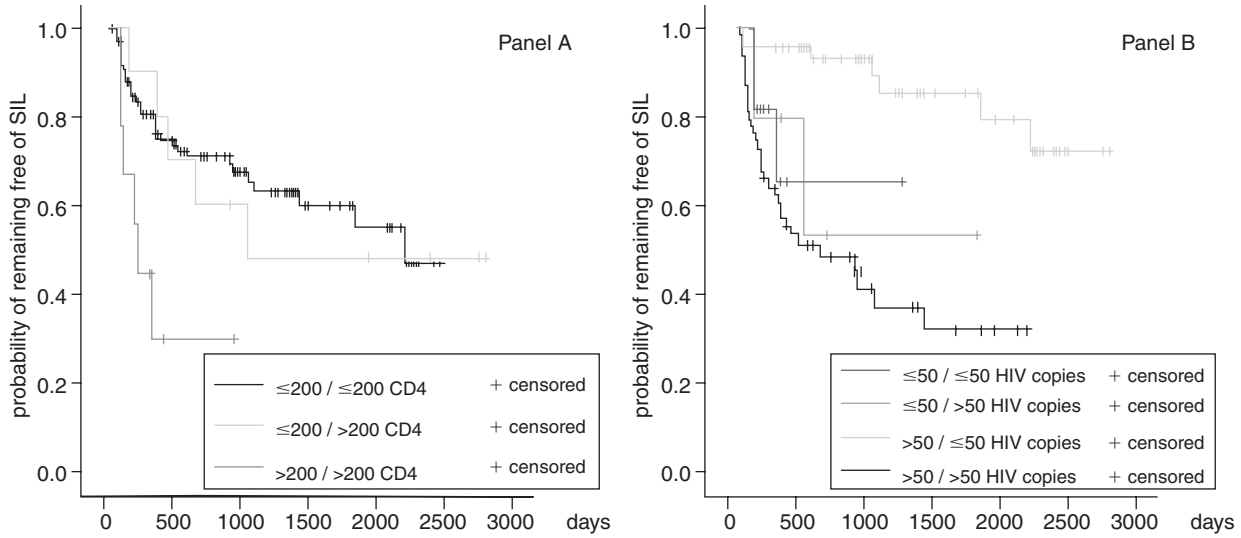

FIG. 2. The actuarial probability (Kaplan-Meier curve) of remaining free of SIL. (**A**) According to the value of baseline and final CD4 lymphocyte count (200 cells/μl). (**B**) According to the value of baseline and final HIV viral load (undetectable $\leq$50 copies).

line group (log rank, $p = 0.04$; Breslow, $p = 0.03$, Tarone–Ware, $p = 0.03$). Similar results were obtained when the patients were stratified by a baseline CD4 cell count of 200. In contrast, SIL was diagnosed only in 12 of 47 (26%) patients with <200 CD4 nadir between cytologies ($p = 0.412$). Similar results were obtained on the cervical cytological evolution when the cut-off of immunological status used was 350 CD4 nadir lymphocyte cells between cytologies.

Effect of HAART on HIV viral load and its impact on cervical cytological evolution

Three patients were lost to this analysis. SIL was diagnosed in 34 of 65 (52%) patients with detectable HIV_VL at baseline and at the final Pap test; in 2 of 5 (40%) with an undetectable baseline HIV_VL but who were detectable at the end; in 7 of 49 (14%) with detectable baseline and undetectable final HIV_VL; and in 3 of 11 (27%) with undetectable baseline and final HIV_VL. So, SIL was diagnosed in 10 of 60 (17%) patients with undetectable HIV_VL between cytologies or with undetectable HIV_VL at the final cytology test, and in 36 of 70 (51%) patients with detectable HIV_VL (OR: 0.19, 95% CI: 0.07–0.46, $p < 0.001$). The distribution of these 70 patients according to their detectable HIV_VLV at final Pap test was 49 patients between >50 and ≤400 copies; 10 patients between >400 and <10,000 copies; and >10,000 copies: 11 patients. Of patients 56% (39 out of 70) presented with bad treatment compliance and 84% (26 out of 31) with treatment resistance. Figure 2B shows the actuarial probability of remaining free of SIL in the patients grouped by baseline and final HIV_VL (log rank, $p < 0.001$; Breslow, $p = 0.001$, Tarone–Ware, $p < 0.001$). Univariate analysis, but not multivariate analysis (Cox regression analysis), showed that an undetectable baseline HIV_VL (OR: 0.13, 95% CI: 0.06–0.31, $p < 0.001$) was an independent predictive factor for remaining free of SIL. Age, age of cervical cytologies, time of HIV diagnosis, CD4 nadir, number of sexual partners, and history of pregnancies were not significantly associated with the risk of developing SILs.

Influence of HAART on the evolution from an ASCUS diagnosis to a normal cervical cytological test (regression) or to SIL or carcinoma (progression)

An ASCUS diagnosis was detected in 55 (41%) patients after previous normal Pap test results. The average time from normal cytology to ASCUS was 737 ± 691 days (min: 99; max: 2275). Only 26 of 55 (47%) patients fulfilled the requirements to study the regression or progression of an ASCUS lesion; for

TABLE 2. NUMBER (PERCENTAGE) OF PATIENTS DIAGNOSED WITH SIL GROUPED BY BASELINE CD4 LYMPHOCYTE COUNT (CELLS/μL)

	CD4 > 500 n (%)	*CD4 ≤ 500* n (%)	*CD4 > 350* n (%)	*CD4 ≤ 350* n (%)	*CD4 > 200* n (%)	*CD4 ≤ 200* n (%)
	18/60 (30.0%)	29/73 (39.7%)	27/90 (30.0%)	20/43 (46.5%)	36/113 (31.9%)	11/20 (55.0%)
OR (95% CI)	0.65 (0.32–1.34), $p = 0.24$		0.49 (0.23–1.04), $p = 0.06$		0.38 (0.14–1.01), $p = 0.05$	

those, only a descriptive analysis was performed. None of these 26 patients with an ASCUS diagnosis progressed to SIL; in 21 (81%) patients the ASCUS lesion regressed to a normal Pap test, and 5 (19%) patients continued to have an ASCUS diagnostic. The average time from ASCUS to a normal Pap test (regression) was 226 ± 205 days (min: 56; max: 974), and the average time from ASCUS to ASCUS (no change) was 317 ± 378 (min: 92; max: 992). Five of these 26 patients were diagnosed as ASC-H (high-grade atypical squamous cells) at baseline, 3 regressed to normal cytology, and 2 maintained the diagnosis at follow-up.

DISCUSSION

Our study has assessed the "natural history" and the incidence of cervical SILs among a cohort of HIV^+ women without a background of cervical pathology. Although this is a retrospective study, and it must be interpreted with caution, our results suggest that the incidence of SIL (cancer precursor lesions) was higher than expected, but that an immunological status of >200 CD4 cells and an undetectable HIV viral load could have a protective role for SIL development.

Limited data are available on the natural history of cervical pathology related to HPV infection in patients on HAART. Some previous data had suggested that about 20% of HIV^+ women without evidence of cervical disease will develop SIL within 3 years.[3–5] In our study, the incidence of SIL was higher than expected (35%) in spite of being a cohort of HIV-infected women treated with HAART. The design of our study, the period of follow-up, races, or geographical differences could overestimate the result obtained. But this result could also suggest, in contrast to other HIV-associated malignancies, that the overall effect of HAART on the course of cervical HPV-related pathology is not clear. Indeed, the long-term effect of HAART on the incidence of cervical pathology is unknown, and its effect on the likelihood of progression to cervical cancer is controversial.[6–15] HIV_VL may involve interactions between HIV and HPV at the molecular level,[20–22] and higher HIV loads have been associated with a reduced likelihood of SIL regression.[23] Then the impact of the effect of HAART on obtaining or maintaining an undetectable HIV_VL status could be related to a reduced incidence of SIL, despite the high incidence of SIL found in our study. As well, our results highlight the fact that improving or maintaining a good immunological status as a consequence of HAART was related to a reduction in the incidence of SIL. That is, immunological status was an important factor in predicting the risk of SILs, suggesting that the boundary of immunodeficiency is between 200 and 350 cells/μl. This finding is consistent with previous studies.[24–26] In fact, HIV-associated cell-mediated immunodeficiency is a factor in predicting the incidence of SILs and in influencing the likelihood of progression of cytological cervical lesions.[27] The immunodeficiency may increase the risk of SILs by permitting HPV persistence,[24,28,29] or by accelerating the transit time to SILs.[30] Actually, SILs are inversely associated with CD4 lymphocyte counts among HIV^+ women.[27]

The etiology and the outcomes of ASCUS are uncertain, as the name implies, and limited data on ASCUS are available.[16–19] Although the small number of patients analyzed in our study did not allow us to derive conclusions, an ASCUS diagnosis was the most common cervical abnormality (incidence of 41% ASCUS diagnosis versus 35% SIL diagnosis), and this result is in accordance with those of a previous study.[19] But, by contrast to this previous study, none of the patients analyzed progressed to SIL and 81% of them regressed to a normal cervical Pap test. These findings could suggest that an ASCUS diagnosis reflects a benign or reactive process, or that HAART could avoid the ASCUS progression in patients previously treated with HAART as well as after the ASCUS diagnosis.

On the other hand, the role of cervical mucosa immunity in HPV-related cervical disease is poorly understood, and a poor immunological status could reflect a bad cervical mucosal immune mechanism important to the natural control of an HPV infection.[31] This study evaluates only the indirect effect of HAART on cervical pathology, as outcome on its effect on immunological status or its effect on HIV viral load. The cervical cytology is the consequence of HPV infection. Thus, it is likely that once the HPV virus genetically alters the epithelial cell, the genetic material of the lesion is irreparable, despite immune recovery or improvement achieved with HAART. That is, in spite of immunological recovery, the epithelial cell cannot revert to a normal healthy state once an SIL has formed.[32] Likewise, this study does not allow the determination of whether HAART has some direct effect on HPV, on epithelial cells, on local immunity, or on the balance between cell proliferation and apoptosis. This is significant because these are important issues that could contribute to the elucidation of the actual role of HAART in this coinfection, in addition to helping to understand why in our cohort the incidence of SIL was higher than expected.

A few limitations of this study should be acknowledged. We have analyzed time until the event (SILs) accepting that the date of the Pap test is the moment that the event is occurring. Our data set was obtained from the database derived from the electronic medical history of HIV^+ outpatients; therefore the data set retrospectively reflected the clinical routine. Although a cervical cytological screening routine is established in our center, we could not assume that all women would adhere to screening and systematic follow-up. Likewise, previous studies have demonstrated that the interpretation of cytological[33] and histological[34] findings are routinely downgraded when they are reviewed by an expert panel.[34,35] All of these factors together could underestimate or overestimate the results obtained.

In conclusion, the results of this retrospective study suggest that although the incidence of SIL (cancer precursor lesions) was higher than expected, the effect of HAART on the control of HIV replication and of immunological status (>200 CD4) through the follow-up is associated with a reduced incidence of SIL among HIV^+ women without a background of cervical pathology. Further prospective studies are necessary to validate our findings.

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