Highly active antiretroviral therapy and incidence of cervical squamous intraepithelial lesions among HIV-infected women with normal cytology and CD4 counts above 350 cells/mm³

Guillem Sirera1,2†, Sebastià Videla2*†, Raquel López-Blázquez3, Mariona Llatjos4, Antoni Tarrats5, Eva Castellà3, Nuria Grane5, Cristina Tural1,2, Celestino Rey-Joly1 and Bonaventura Clotet1,2

1HIV Clinical Unit, Department of Medicine, University Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona (U.A.B.), Badalona (Barcelona), Spain; 2Lluita Contra La SIDA Foundation, University Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona (U.A.B.), Badalona (Barcelona), Spain; 3Department of Statistics, Universitat Politècnica de Barcelona, Barcelona, Spain; 4Department of Pathology, University Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona (U.A.B.), Badalona (Barcelona), Spain; 5Department of Gynecology, University Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona (U.A.B.), Badalona (Barcelona), Spain

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Objectives: To provide evidence for the long-term effect of highly active antiretroviral therapy (HAART) on the incidence of cervical squamous intraepithelial lesions (SILs) among HIV-positive women with normal cytology test and CD4 count above 350 cells/mm³.

Patients and methods: A retrospective cohort study was carried out in HIV-positive women with two consecutive normal cervical cytological tests (Papanicolaou test) and at least one subsequent test, without previous cervical history of SIL or cancer diagnosis, and with an immunological status >350 CD4 cells/mm³. The patients were divided into two groups: treated with HAART (HAART group) or not treated with HAART (NO-HAART group), during the period of time between cytology tests included in the survival analysis and time until SIL.

Results: Between January 1997 and December 2006, 127 women were included: 90 in the HAART group and 37 in the NO-HAART group. Both groups of patients were similar with respect to demographic data, except for HIV viral load and previous HAART inclusion (P < 0.001). SIL was diagnosed in 27 of 90 (30%) patients in the HAART group and in 7 of 37 (19%) patients in the NO-HAART group (OR = 1.84, 95% CI: 0.72–4.69, P = 0.202). The actuarial probability of remaining free of SIL at 3 years was 70% in the HAART group and 78% in the NO-HAART group. No variable was associated with an increased risk of developing SILs.

Conclusions: These results suggest that when the patients’ immunological status is above 350 CD4 cells/mm³, the HIV-infected women treated with HAART present a similar cervical SIL incidence to women not on HAART.

Keywords: HAART, immunological status, cervical SIL in HIV, women

Introduction

It is accepted that the necessary cause of cervical squamous intraepithelial lesions (SILs), which are precursors of invasive cervical cancer, is human papillomavirus (HPV) infection.1,2

*Corresponding author. Tel: +34-609-059-287; Fax: +34-93-465-76-02; E-mail: svidela@esteve.es
†These authors contributed equally to this study.

Previous reports have suggested that ~20% to 35% of HIV-infected women without previous evidence of cervical disease will develop SIL within 3 years.3,4

Highly active antiretroviral therapy (HAART) has greatly reduced morbidity and mortality in HIV patients, but its effect...
on the evolution of cervical cytological changes in HIV-positive women is full of controversy.\textsuperscript{3–5} Currently,\textsuperscript{6} HAART is recommended when the immunological status is lower than 350 CD4 cells/mm\textsuperscript{3} but it is not known whether HAART could have an effect on the evolution of cervical cytological changes when the immunological status is above 350 CD4 cells/mm\textsuperscript{3}. Therefore, the objective of this retrospective cohort study, based on the cohort of female outpatients treated by the gynaecologists (A. T. and N. G.) in the HIV Unit at the University Tertiary Hospital, was to provide data on the long-term effect of HAART on the incidence of cervical SIL among HIV-infected women with a normal baseline cytological test, without previous history of cervical pathology, and with an immunological status >350 CD4 cells/mm\textsuperscript{3}.

Patients and methods

Between January 1997 and December 2006, all women included in a compiled database (electronic medical files) 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 to include patients in the study.

The patients included in this study had to fulfil the following eligibility criteria: women with an HIV infection diagnosis and two consecutive normal cervical cytological tests (Papanicolaou test, Pap) and at least one subsequent test; no previous history of cervical dysplasia or cancer diagnosis; and a baseline immunological status above 350 CD4 cells/mm\textsuperscript{3}. The date of the first normal Pap test was considered the baseline moment.

The following data were also gathered at baseline: date of birth, dates of cervical cytological tests, date of HIV infection diagnosis, CD4 cells/mm\textsuperscript{3} (+1 month from the date of normal Pap), CD4 nadir previous to inclusion, HIV viral load (HIV_VL) (+1 month from the date of normal Pap), HAART prior to inclusion, number of sexual partners, number of patients with history of pregnancies and other risk factors such as intravenous drug abuse, and history of smoking. Between cytological tests, the following information was collected: CD4 nadir, CD4 cells/mm\textsuperscript{3} (+1 month from the date of Pap), HIV_VL (+1 month from the date of Pap) and 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 non-nucleoside reverse transcriptase inhibitor.

The Pap test was the standard diagnostic technique used routinely in gynaecological examination. The cytological changes were classified according to the Bethesda System. Most samples were checked by two cytopathologists (M. L. and E. C.). When a patient was diagnosed with an SIL (low- or high-grade, LSIL or HSIL, respectively), a colposcopy and a biopsy were proposed in order to verify the cytological result.

The primary endpoint of the study was SIL diagnosis, and to study the influence of HAART on SIL incidence during follow-up, the patients were divided into two groups according to whether they were being treated with HAART (HAART group) or not being treated with HAART (NO-HAART group) for the period between baseline and final cytological tests.

Statistical analysis

A descriptive analysis was performed by baseline population. Continuous data are summarized as mean (SD: standard deviation) (minimum and maximum).

The evolution of cervical cytology (SIL incidence during follow-up) was studied with the Kaplan–Meier curves and the differences were assessed with the log-rank test. The bivariate and multivariate proportional hazard regression (Cox regression) analyses were performed to determine which of the following factors would predict SIL: age, age of cervical cytology, time of HIV diagnosis, baseline CD4, CD4 nadir (previous inclusion and between cytology tests), HIV_VL, HAART previous inclusion, number of partners, number of pregnancies and other risk factors such as intravenous drug abuse, and tobacco use. Odds ratios (OR) and hazard ratios (HR) comparing SIL diagnosis and their corresponding 95% confidence intervals (CIs) were estimated. A P value of \textless{}0.05 was considered statistically significant.

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

Results

The study included 127 women (35 ± 9 years old): 90 in the HAART group and 37 in the NO-HAART group. Both groups of patients, HAART and NO-HAART, were similar with respect to demographic data (Table 1), except for HIV viral load and previous HAART inclusion (P < 0.001); only one patient in the NO-HAART group had previously received HAART. The average time to SIL development was 1836 days (95% CI: 1616–2096), and the average number of Pap smears (+SD) between baseline and final Pap test was 4.1 ± 2.8 (range 1–14).

SIL was diagnosed in 27 (24 LSIL and 3 HSIL) out of 90 (30%) patients in the HAART group and in 7 (6 LSIL and 1 HSIL) out of 37 (19%) patients in the NO-HAART group (OR = 1.84, 95% CI: 0.72–4.69, P = 0.202). The actuarial probability of remaining free of SIL at 3 years was 70% in the HAART group and 78% in the NO-HAART group. Figure 1 shows the actuarial probability (Kaplan–Meier curve) of remaining free of SIL in the HAART and NO-HAART groups (log rank, P = 0.387). No variable was associated with the risk of developing SILs. HRs (95% CI) for the bivariate proportional hazard regression were for age 1.04 (0.98–1.10), CD4 1.00 (0.98–1.01), HIV viral load 1.00 (0.99–1.01), time since HIV infection diagnosis 0.98 (0.89–1.08) and HAART 1.44 (0.67–3.32). HRs (95% CI) for the multivariate proportional hazard regression were for CD4 1.00 (0.99–1.01) and HAART 1.66 (0.16–16.85).

Sixteen patients presented an immunological status lower than 350 CD4 cells/mm\textsuperscript{3} during the follow-up; 9 (10%) patients in the HAART group and 7 (18.9%) in the NO-HAART group (P = 0.169). Only 2 (28.6%) of the 7 patients from the NO-HAART group developed an SIL.
Discussion

This study is different from previous research because it presents the effect of HAART on the ‘natural history’ of cervical SILs among a cohort of HIV-positive women without a background of cervical pathology and with an acceptable immunological status. Unlike other infections in HIV-positive patients, HPV infection evolves to cancer after many years without symptomatology. Several limitations of our study must be acknowledged: the retrospective observational design (non-randomized), the small sample size and the assumption that the date of the Pap test is the time that the event occurred. These factors are not ideal for evaluating the impact of HAART on the natural history of cervical pathology, and all of these factors together could cause our results to underestimate or overestimate the real effects. Our results suggest that when the patient’s immunological status is above 350 CD4 cells/mm$^3$, HIV-infected women treated with HAART presented a similar cervical SIL incidence to women not on HAART. Although the effect of HAART on the evolution of cervical cytological changes in HIV-positive women is full of controversy, our results are in agreement with other reports. Likewise, this result is along the lines of other HPV-related pathologies, for example, the incidence of oral and cutaneous warts is higher in HIV patients treated with HAART.

We have compared populations with a similar quantitative immunological status, but we cannot dismiss that these groups are different in qualitative immunological status. In the NO-HAART group, only one patient had received HAART prior to the study, and only seven patients were candidates to receive HAART during the study. This could indicate that these patients had a priori different risks of developing SIL. Other possible explanations could be that HAART therapy alters the cervical immunology, or HAART therapy could have a toxic effect on epithelial cells and/or causes an imbalance between cell proliferation and apoptosis.

In conclusion, our findings suggest that HAART did not have a specific effect on the reduction of cervical SIL incidence in the group of HIV-positive women without a background of cervical pathology and with an acceptable immunological status (>350 CD4 cells/mm$^3$). Therefore, it is necessary to emphasize that HIV-positive women are candidates for closer monitoring of cervical pathology. Further prospective studies are required to validate our findings.

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Transparency declarations

S. V. has received honoraria for collaborating with Laboratorios Dr Esteve. B. C. has received honoraria for speaking and participating in advisory boards from Abbott, Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead Sciences, GlaxoSmithKline and Pfizer.

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