

High Recurrence Rate of Cervical Dysplasia and Persistence of HPV infection in HIV-1-infected Women

ANDREA GINGELMAIER, THOMAS GRUBERT, RALPH KAESTNER, IOANNIS MYLONAS, TOBIAS WEISSENBACHER, FLORIAN BERGAUER, LISA BARTHELL and KLAUS FRIESE

First Department of Obstetrics and Gynecology, Ludwig-Maximilians University, Munich, Germany

Abstract. *Aim: a) evaluation of the recurrence of cervical dysplasia after surgical treatment and of the rate of HPV persistence of HIV-infected women and b) the influence of antiretroviral therapy on the recurrence. Patients and Methods: In a retrospective analysis, the follow-up data of HIV-positive women visiting our outpatient clinic regarding results of cervical cytology, cervical HPV detection, cervical biopsy, patient history of dysplasia and antiretroviral therapy were assessed. A total of 388 HIV-positive women had a mean follow-up of 2.7 years and a median of 2.5 outpatient visits. Results: Out of the 344 patients (57.3%) tested for HPV, 197 showed at least one positive HPV result. Of the same group, 136 women had four or more HPV tests which showed that 84 of them (61.8%) had a persistent HPV-infection. Overall, 157/388 had cervical dysplasia and 70 needed surgery. Forty-one of the 70 patients (58.6%) received more than one surgical treatment because of a recurrence, all of this group had persistent HPV. Discussion: The recurrence of cervical dysplasia in HIV-positive women after surgical treatment was found to be very high as was the associated long-term persistence of HPV-infection. HPV persistence represented an excellent marker for relapsing cervical dysplasia.*

Due to antiretroviral therapy (ART), the life expectancy of HIV-1 positive women increased substantially during the past decade (1). As a consequence of the longer survival, HIV-1 has become an important risk factor for human papillomavirus (HPV) infection and the development of HPV-associated lesions in the female genital tract (2, 3). According to the Center for Disease Control and Prevention,

cervical cancer represents an AIDS-defining illness in HIV-infected women (4). The antiretroviral treatment of HIV-positive women was supposed to prevent the HPV-associated development of a cervical cancer or dysplasia due to a reconstitution of the immune system (5). However due to a lack of data, it remains unclear if the administration of ART is also able to ameliorate the course of anogenital HPV-infections and anogenital dysplasia (6). Therefore, the aims of this study were the evaluation of: (a) the recurrence rate of cervical dysplasia after surgical treatment and the rate of HPV persistence; (b) the influence of an antiretroviral therapy on the recurrence rate.

Patients and Methods

This retrospective analysis was performed using patient data collected over the past ten years at a specialized gynecological outpatient clinic for HIV-positive women at the University of Munich. The history of previous dysplasia was assessed and every result of a cervical cytology, cervical HPV detection (low-risk, high-risk), cervical biopsy or surgical treatment with the corresponding histology was documented. The antiretroviral therapy and virological/immunological parameters (viral load, CD4 count) were registered on every visit when available. Cervical smears were performed in-house using a cytobrush and a conventional cytology. Cervical HPV detection was conducted using Hybrid Capture® 2 from Digene (or a reverse line blot HPV-genotyping assay) according to the recommendations of the manufacturer. The baseline characteristics of the examined cohort were the following: 388 HIV-positive women with a mean follow-up of 2.7 years (range 0-16 years, median 3.6 years) with a median of 2.5 outpatient visits (range 1-58, mean 8.7). The mean age at the first visit was 30.1 years (range 15.3-59.3 years, median 23.3 years). The course of horizontal transmission was most frequently heterosexual and/or originating from an endemic region (together 59.4%). Statistical analysis was performed using SPSS version 12.0 software (SPSS Inc.).

Results

Of the 388 HIV-positive women visiting our outpatient clinic, 31 (8%) reported a history of cervical dysplasia. During the follow-up visits the 357 patients without a preceding dysplasia showed an incidence of 36% for cervical

Correspondence to: Andrea Gingelmaier, First Department of Obstetrics and Gynecology, Ludwig-Maximilians University (Director: Prof. Dr. med. K. Friese), Maistrasse 11, 80337 Munich, Germany. Tel: +49 89 5160 4111, Fax: +49 89 5160 4580, e-mail: andrea.gingelmaier@med.uni-muenchen.de

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Table I. *Histological results of the surgical procedures.*

Histology	n	%
Negative	6	4.8
CIN I	39	31.2
CIN II	19	15.2
CIN III	59	47.2
Cervical cancer	2	1.6
Total	125	100

CIN: Cervical intraepithelial neoplasia.

dysplasia (126 cases). Of the 31 women with a history of dysplasia, 28 (90%) experienced a recurrence. This demonstrates a recorded rate of cervical dysplasia in this cohort of 30.4% (157/388) overall. Of 388 HIV-positive women, 344 had results of cervical HPV-testing: 57.3% (197/344 patients) were found to be positive for high-risk HPV on at least one visit. One hundred and thirty-six women of that cohort were examined at least four times or more regarding genital HPV and 24.4% (84 patients) had persistent high-risk HPV, which was defined as testing positive on not less than two occasions for high-risk HPV. Furthermore, 10.5% of this group (36/84 patients) had a long-term persistence of HPV with a range of 5 to 23 positive high-risk HPV results.

Seventy patients of this cohort underwent a surgical treatment such as a cone biopsy because of a cervical cytology and colposcopy suggesting a high grade squamous intraepithelial lesion (SIL). Forty-one of them (58.6%) underwent more than one procedure because of a recurrent dysplasia. The histological results of these surgical interventions (n=125) are shown in Table I. Two cervical cancer cases were detected. All women with a proven recurrency showed a persistent high-risk HPV-infection. Before the first surgical intervention there were 150/388 patients (29%) who presented a suspect cervical cytology and 194/388 patients had a positive high-risk HPV-test. The follow-up of 47 of these women after surgery found suspect cytology and evidence of a persistent high-risk HPV in 36 (76.6%). The risk of developing a cervical dysplasia is highly correlated with a persistent high-risk HPV detection. This correlation is shown in Figure 1, where the odds ratio for dysplasia increases with the number of consecutive detections of high-risk HPV. For 313/388 HIV-infected women, data was available regarding their antiretroviral therapy and virological/immunological parameters: 229 of them had never taken any antiretroviral therapy and 84 were on 1 to 5 different drugs in their regimen. The mean of the assessed values of the viral load and CD4 count of the individuals and the median in the two groups of these patients were calculated. Table II shows a comparison between these

Table II. *Influence of ART (antiretroviral therapy).*

	Not taking ART (n=229)	Taking ART (n=84)
CD4/ μ l (median)	496	317
Viral load copies/ml (median)	3765	1062
Suspect cytology (%)	33.6	82.9
High-risk HPV (%)	50	80.8

Table III. *Risk of recurrence with or without antiretroviral therapy.*

	Not taking ART	Taking ART	Total
No recurrence	3 (37.5%)	8 (20.5%)	11 (23.4%)
Recurrence	5 (62.5%)	31 (79.5%)	36 (76.6%)
Total	8 (100%)	39 (100%)	47 (100%)

two groups regarding viral load, CD4 count, incidence of suspect cytology and detection of high-risk HPV. Examining the data for the 47 patients with a recurrence after surgery, it can be seen from Table III that taking an ART correlates with a higher risk of a relapse (OR 2.3 (0.5-11.9)).

Discussion

Many studies have shown a higher prevalence of cervical dysplasia in a cohort of HIV-1 positive women compared to HIV-negative women (2, 7). This is consistent with our findings of a rate of 30.4% of cervical dysplasia in this group overall. The Women's Interagency HIV Study [WIHS (2)] revealed that risk factors for any abnormal cytology in a multivariate analysis included HIV infection, low CD4 cell count, high HIV-RNA level, detection of human papillomavirus, a prior history of abnormal cytology, employment, and number of male sex partners within 6 months of enrollment. The frequent persistence of HPV-infections in HIV-positive women was also shown in a prospective study in New York (8) where 24% of the HIV-infected women had a persistent HPV compared to 4% of the HIV-negative group. Our data also detected a high rate (10.5%) of very long persistence, up to 23 examinations (with an interval of at least 2-3 months between them). The crux of the matter is the high recurrence rate for HIV-infected women, even after excisional procedures such as LEEP (Loop Electrosurgical Excision Procedure) or a cone biopsy combined with laser treatment: 58.6% of the patients underwent more than one surgical treatment and the follow-up of 47 individuals after surgery again revealed a suspect cytology in 76.6%. None of the patients who experienced a

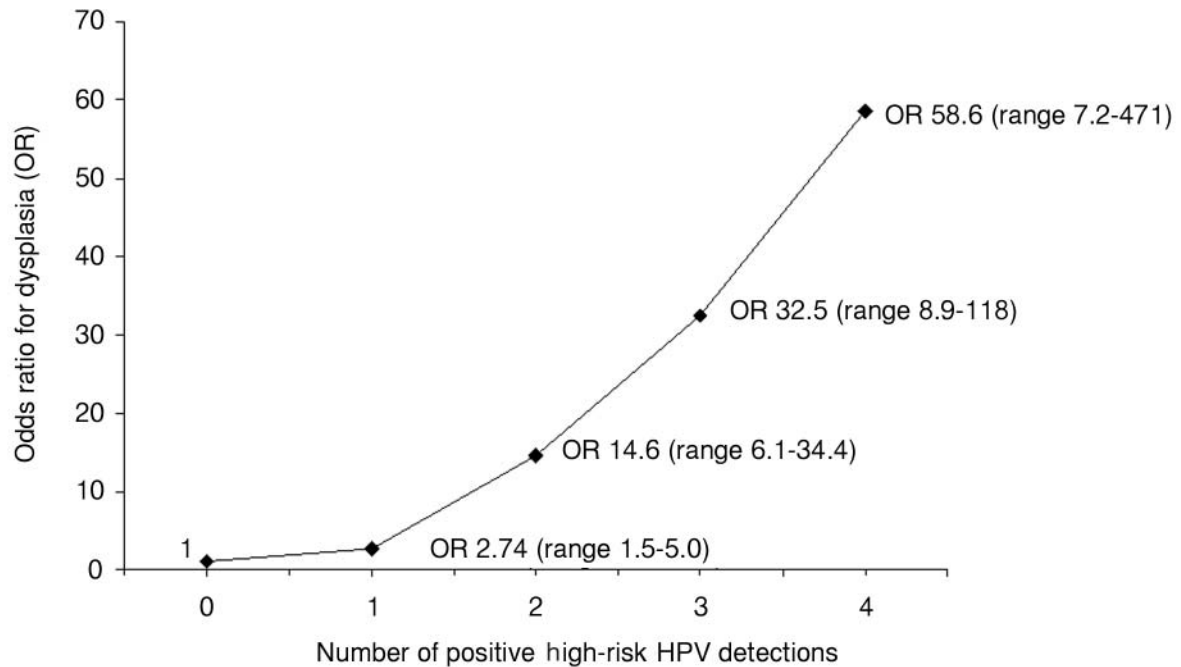


Figure 1. Correlation between high-risk HPV detection and development of cervical dysplasia.

recurrence reported negative regarding high-risk HPV. Therefore persistent high-risk HPV after surgical treatment presents an excellent marker for the prediction of a relapse. The increasing risk of developing a cervical dysplasia with the number of consecutively detected high-risk HPV supports this.

The influence of antiretroviral therapy or highly active antiretroviral therapy (HAART) on the course of anogenital dysplasia is controversial in the literature. ART is likely to improve the immune system of HIV-infected individuals associated with an increasing CD4 count, and therefore is supposed to ameliorate the suppression of an HPV-infection and the regression of a cervical dysplasia as well. For example, an Italian study showed no difference in persistence of high-risk-HPV infection and progression of dysplasia after initiation of HAART over a mean of 15 months, despite increasing CD4-count (9), whereas in the WIHS (10) HAART statistically reduced the progression and increased the regression of these kind of lesions, though the effect was small. There are several other reports who found different results as reviewed recently by Palefsky (11) who states that the beneficial effects of HAART are relatively modest but that the understanding of this influence remains poor.

Comparing our two groups of taking or not taking ART, the difference between the higher rate of suspect cytology and high-risk HPV infection in the ART-taking group is presumably due to the lower CD4 count associated with a more advanced immune deficiency in this group. This is

consistent with our finding that these patients had a higher rate of recurrence after surgery (79.5% vs. 62.5%). A recent study (12) in this context showed that a low CD4 count was a predictor for recurrence after surgery and the investigators concluded that surgery in HIV-positive women is only effective in preventing cancer. Therefore we conclude that HIV-infected women should be monitored frequently using cervical cytology/colposcopy and HPV-testing, ideally in a long-term care situation, to prevent an emerging anogenital cancer.

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