# Long-term effectiveness of electrocautery ablation of HGAIN in HIV-infected MSM.

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## INTRODUCTION

• The incidence of anal cancer is about 65–130 cases per 100000 person-years in HIV -infected men who have sex with men (MSM).
• Anal cancer, in the same way that cervical cancer, is associated to infection by oncogenic human papillomavirus (HPV) at the squamocolumnar transition zone, and it is believed to arise from precancerous dysplasic lesions, called high-grade anal intraepithelial neoplasia (HGAIN).
• Experience with treatment of cervical cancer shows that treatment of dysplasic lesions could be the best way to modify the natural progression of the disease and thus avoid the development of invasive carcinoma.
• There are different treatment options for treatment of HGAIN lesions, including topical agents (imiquimod, 5-fluorouracil and trichloroacetic acid) and ablative procedures (infrared coagulation and electrocautery). Recently, an open-label randomized trial in HIV-infected MSM has shown that electrocautery ablation is better than topical imiquimod or fluorouracil for the treatment of AIN.

## OBJECTIVES

The aim of our study is to evaluate the long-term effectiveness and safety of electrocautery ablation for the treatment of HGAIN in a cohort of MSM with HIV-infection.

## MATERIAL and METHODS

**Population:**
▪The Screening and Treatment of Anal Dysplasia Unit was created at the University Hospital Vall d'Hebron (Barcelona, Spain) in May 2009. All MSM with HIV-infection attending the HIV units from this hospital and the University Hospital del Mar (Barcelona, Spain) were informed about the screening program and participation was actively encouraged.
▪ All the HIV-infected patients included gave informed consent to use information available in the electronic database and medical records. The study was approved by the Commission of Medical Ethics of the Hospital Vall d'Hebron (PR[AG]240/2014).

**Procedure of anal dysplasia screening**
▪ The anal dysplasia screening included an anal cytology followed by a digital ano-rectal examination and HRA in each visit.
▪ Cytology was obtained by introducing a Dacron swab 3-5 cm into the anal canal and gently rotating it for 30-45 seconds. The swab was introduced into 20 ml of PreservCyt/ThinPrep Pap test solution (Cytyc-Iberia, Spain) and shaken for 30 seconds. This sample was used to carry out the cytological analysis and HPV testing.
▪ HRA was performed using a technique described elsewhere, including the topical application of 3% acetic acid and lugol solution in the anal canal . The anal biopsy was performed on suspicious intra-anal lesions revealed by HRA. Anal samples from the histology examination were classified as normal, low-grade AIN (LGAIN), high-grade AIN (HGAIN), or squamous-cell carcinoma (SCC), in accordance with the Bethesda classification .

**Procedure of anal dysplasia treatment**
▪ Treatment with electrocautery was offered to patients with HGAIN lesions confirmed by histological examination.
▪ Ablations of lesions were performed using the ARC350 Electrosurgical Unit (Bowa, Germany) on 20-30 watts with 2-5 mm spheres. All visible lesions were treated in the same session if the extension was less than a quarter circumferences. Infiltration of 0.5% bupivacaine was used to achieve local anesthesia.
▪ Electrocautery was done every 4-6 weeks for a minimum of two sessions or until visual inspection revealed lesion regression after a maximum of four sessions. The two-to-four electrocautery sessions were considered as a cycle of treatment.
▪ Following the completion of the ablative cycle of treatment, 6-8 weeks after the last electrocautery session, patients underwent a new evaluation involving visual inspection with HRA and an anal biopsy. Histological samples were taken from the areas where AIN had previously been reported and, if necessary, from other suspicious lesions.
▪ Patients with post-ablation biopsy-proven HGAIN were advised to undergo a further cycle of electrocautery treatment. Patients with normal or LGAIN histology post-ablation were monitored with anal cytology and HRA examinations at 6-to-12-month intervals.

**Study definitions**
▪ The effectiveness of electrocautery ablation was evaluated for:
a) each patient or complete treatment: including all necessary treatment cycles until a response was achieved, or until the end of follow-up; and
b) each cycle of treatment: including 2-4 electrocautery sessions.

▪ Only patients completing at least one cycle of electrocautery and post-ablation biopsy were included in analysis.
▪ Complete response was defined as the resolution of AIN on the post-treatment biopsy and partial response as regression from high-grade to low-grade AIN. Persistence was considered when an unmodified HGAIN lesion was identified in a biopsy sample obtained from the treated anal area.
▪ Recurrence was defined as biopsy-proven HGAIN at the treated site or at a new site in the follow-up in patients with complete or partial response. Time to recurrence was measured from the end of electrocautery treatment to the date when the recurrent HGAIN was diagnosed.

## MATERIAL and METHODS

**Statistical Analysis**
Categorical variables were described as numbers (percentage) and continuous variables as median (interquartile range, IRQ), unless otherwise specified. A Student's T-test or U de Mann-Whitney for paired data was used for quantitative variables and $c^2$ test or McNemar test was performed to compare categorical variables. The effectiveness of electrocautery was evaluated using on-treatment analysis, where patients who interrupted treatment or were lost to follow-up were censured, and expressed as a percentage and 95% confidence intervals. The time to recurrence was analyzed using the Kaplan-Meier method. Factors associated with response to treatment and recurrence of HGAIN were evaluated using logistic regression methods. IBM SPSS statistics software for Windows (Version 19.0) was used for the statistical analyses.

## RESULTS

**Patients' characteristics**
▪ From May 2009 to November 2014, 126 (21.9%) of the 576 patients who participated in the screening program presented or developed HGAIN lesions.
▪ The median age of patients was 41.2 (IRQ: 34.1-45.9), with a median duration of HIV-infection of 4.9 years, and 81% were receiving HAART. The baseline CD4 cell count was 600 (IRQ: 408-789) cells/µL and 65.6% had an undetectable HIV load.

| | Global (n=126) | Responding patients (n=55) | Non-responding patients (n=28) | P value |
|---|---|---|---|---|
| **Sociodemographic variables** | | | | |
| Age, years | 41.2 | 42.4 | 41.8 | .86 |
| Current smokers | 31% | 23.4% | 42.9% | .12 |
| **HIV-infection related variables** | | | | |
| Time since HIV diagnosis, years | 4.9 | 5.1 | 7.4 | .08 |
| Current CD4 cell count, cells/µl | 600 | 597 | 645 | .21 |
| Nadir CD4 cell count, cells/µl | 287 | 284 | 286 | .95 |
| Undetectable plasma HIV-RNA | 65.6% | 66% | 72.4% | .61 |
| HAART therapy | 81% | 82.4% | 82.8% | .72 |
| Time on ART treatment, years | 3.15 | 3.9 | 7.1 | .17 |
| **Sexual behavior** | | | | |
| Age at first sexual intercourse, years | 17 | 17.5 | 18 | *.86* |
| Lifetime no. of sexual partners | 175 | 200 | 200 | *.9* |
| Current stable sexual-partner | 43.9% | 54.8% | 52% | *.73* |
| Routine use of condom | 85.4% | 80% | 87% | *.59* |
| History of venereal diseases | 71.6% | 71.1% | 77.8% | *.59* |
| Oncogenic HPV detected | 91.3% | 88.2% | 100% | *.08* |
| 16 or 18 HPV detected | 66.9% | 63% | 69% | .62 |

**Electrocautery effectiveness**
▪ During the period of study, 108 patients out of 126 with HGAIN lesions received treatment with electrocautery ablation. The remaining patients refused treatment, were lost to follow-up or have not started treatment yet.
▪ Twenty-five of the patients treated were excluded from the final analysis because they were either lost to follow-up (n=4), had no post-treatment biopsy (n=9) or did not complete the first cycle of treatment (n=12).

**Effectiveness of electrocautery ablation treatment for HGAIN**

| | Complete response % (95% CI), n | Partial response % (95% CI),n |
|---|---|---|
| Patient treatment | 32.5% (23.4-53.2), 27/83 | 33.7% (24.5-44.4), 28/83 |
| Cycle of treatment | 23.9% (17-32.5), 27/113 | 24.8% (17.7-33.5), 28/113 |

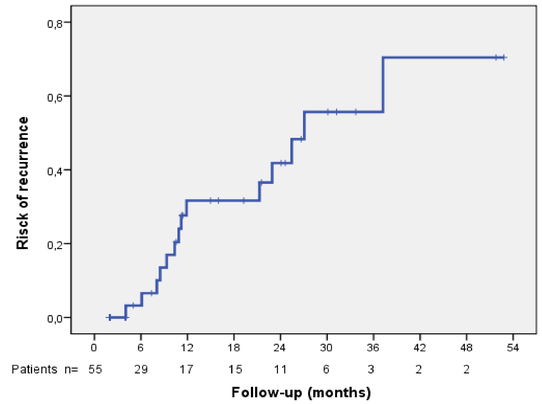
▪The effectiveness of electrocautery was evaluated in 83 patients. Of these, a complete response was observed in 27 (32.5% [95% CI; 23.4-53.2]), a partial response in 28 (33.7% [95% CI; 24.5-44.4]) and persistence in 28 patients (33.7% [95% CI; 24.5-44.4]).

## RESULTS

▪ The effectiveness of the 113 evaluable cycles of treatment was evaluated, we observed a complete response in 23.9% of cases (95% CI; 17-32.5), partial response in 24.8% (95% CI; 17.7-33.5) and non response in 51.3% of cycles (95% CI; 42.2-60.3).
▪The most successful patients only required one cycle of treatment (81.8%). The probability of treatment response to a first cycle of electrocautery was 54.2% (95% CI, 43.5-65.5). If there was no initial response, the probability of success for a second cycle was 35% (95% CI; 18.1-56.7), diminishing to 25% (95% CI, 7.1-59.1) for a third treatment cycle.
▪ No patient treated (including the three patients with history of previous invasive SCC) progressed from HGAIN to invasive anal cancer during the follow-up study.

**Recurrence of the HGAIN**
▪ After a mean follow-up of 12.1 months (IRQ: 2-21.3), 14 of the 55 patients (25.4%, 95% CI; 15.8-38.3) with a response developed recurrent HGAIN with a mean time to recurrence of 29.9 (95% CI; 22-37.7) months.
▪ The probability of recurrence was 27.6% at 12 months (95% CI; 11.3-43.9) and 48.3% at 24 months (95% CI, 27.1-69.5).

**Recurrence of HGAIN after electrocautery ablation treatment**




**Safety of electrocautery**
▪ No patients developed serious adverse events (anal stricture, persistent bleeding or failure to heal) after electrocautery treatment.
▪ Mild pain was the most common post-electrocautery event (42.2%, 35/83), lasting less than 3-5 days and was adequately controlled with mild analgesics. Limited bleeding was the second common adverse event, occurring in 15.7% (13/83) of cases. No patient required the interruption of treatment due to side-effects.

**Risk factor to successful treatment and recurrence**
▪ No significant differences were observed regarding HIV-infection or sexual behavior related variables when comparing patients with a response to patients with persistent HGAIN; neither were factors associated with recurrence found.

## CONCLUSIONS

▪ Although electrocautery is currently the standard treatment for anal dysplasia, its effectiveness is limited, with a low percentage of response and high rates of recurrence.
▪ New treatment strategies are required to achieve the optimum management of patients with anal dysplasia.