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**Angaben zur Veröffentlichung / Publication details:**

Todorova, A., V. Schwierzeck, D. Turek, A. Zink, C. Schwerdtfeger, K. Kaliebe, C. D. Spinner, and Claudia Traidl-Hoffmann. 2019. "Evaluation of anal carcinoma screening in male and female HIV patients at an interdisciplinary HIV therapy centre." *Journal of the European Academy of Dermatology and Venereology* 33 (8): 1595–1601. https://doi.org/10.1111/jdv.15575.



# Evaluation of anal carcinoma screening in male and female HIV patients at an interdisciplinary HIV therapy centre

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## Abstract

**Background** Incidence of anal carcinoma is increased in people living with HIV (PLWH). Due to the improved life expectancy in PLWH, identifying appropriate prevention strategies for non-AIDS-defining cancer types such as anal carcinoma has become a priority in managing PLWH today.

**Objective** We aimed to evaluate anal cytology assessment as screening tool for anal dysplasia and/or carcinoma in PLWH, regardless of gender or sexual orientation. Additionally, we investigated the correlation between cancer risk factors and abnormal screening results in our patient cohort.

**Methods** People living with HIV from the Interdisciplinary HIV Centre of the University Hospital rechts der Isar in Munich, Germany (IZAR), were screened for anal carcinoma by single cytobrush examination and anal Papanicolaou (PAP) smear assessment from 2013 to 2015. Patients with abnormal PAP smear result were offered a follow-up examination after 12 months. Differences between two groups were tested for statistical significance using Student's *t*-test and Mann–Whitney *U*-test, as appropriate.

**Results** In total, 101 PLWH were included. 26.7% of subjects ($n = 27$) were PAP IIID, and 9.9% ($n = 10$) were PAP IVa. Seven female subjects had an abnormal finding at screening. Smoking was significantly associated with abnormal findings at screening ($P = 0.005$). In addition, our study found an association between sexually transmitted infections (STI) and anal dysplasia. Condylomata acuminata were increased in subjects with PAP IIID/PAP IVa ($P = 0.045$). Reactive syphilis serology was found to be significantly associated with abnormal screening results ($P = 0.016$), respectively.

**Conclusion** Our results demonstrate that smoking and two common STIs, condylomata acuminata and syphilis, are risk factors associated with advanced anal intraepithelial neoplasia (AIN) stages in our PLWH cohort. While further analysis is needed to determine diagnostic guidelines concerning AIN in PLWH, these results suggest that interdisciplinary lifestyle prevention strategies are required to reduce the risk factors for AIN in PLWH in an outpatient setting.

## Conflict of Interest

The authors declare no potential conflict(s) of interest.

## Funding Sources

None.

## Introduction

Since the introduction of antiretroviral therapy (ART) for HIV infection, a changing spectrum of cutaneous and general diseases occurs along with the extended life expectancy in people living with HIV (PLWH).[1,2] During the last twenty years, the main prevention and treatment focus of concomitant diseases has shifted from AIDS-defining diseases to non-AIDS-defining diseases. Most common among them are cardiovascular diseases and non-AIDS-defining malignancies such as lymphomas, squamous epithelial carcinomas, and lung and liver cancer.[3–7] Lymphomas and squamous epithelial carcinomas have been described as diseases with higher prevalence among PLWH.[6,7]

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While squamous epithelial anal carcinoma shows with 0.3–1/100 000 cases per year a relative low incidence in the general population, the incidence is 40- to 50-fold higher in patients with HIV including an accelerated course of disease and earlier manifestation.[8,9] Clinical studies have shown that a chronic mucosa infection with high-risk human papillomavirus (HPV) represents an important associated risk factor for the development of anal intraepithelial neoplasia (AIN) and anal carcinoma.[6,10] Current data highlight the prevalence of anal HPV infections with high-risk HPV in up to 90% in PLWH and men who have sex with men (MSM).[11–14] Moreover, chronic genital viral or bacterial infections seem to promote a chronic inflammation and the development of dysplastic lesion.[6,11] Similar to other common squamous carcinomas, there is strong evidence for the impact of smoking as a risk factor with up to 7-fold increased incidence of high-grade AIN.[15] Several studies have linked impaired immune function, such as low nadir CD4 cell count or low CD4/CD8 ratio, with HPV infection, which is itself a risk factor for anal carcinoma.[12,16]

Due to the increased incidence of non-AIDS-defining malignancies in PLWH compared to age-matched controls, screening approaches for prevention or early diagnosis of anal mucosal dysplasia have been discussed for PLWH of both genders.[7,8,17,18] National and international guidelines as well as recent studies recommend an annual proctologic examination for PLWH.[19–21] High-resolution anoscopy (HRA) also has been proposed as initial method of screening for PLWH.[22] And there is evidence that cytological PAP smear as a prevention tool for anal carcinoma in PLWH offers a favourable cost–benefit ratio depending on healthcare setting.[23]

The aim of this study was to evaluate cytological anal PAP smear screenings for PLWH in the setting of a HIV outpatient clinic and to monitor risk factors in this cohort.

## Materials and methods

### Study cohort

People living with HIV with documented HIV infection, aged above 18 between 2013 and 2015, were screened at the Interdisciplinary HIV Therapy Centre of the University Hospital rechts der Isar in Munich and consecutively enrolled after written informed consent. The study was counselled and approved in the local Institutional Review Board/ethics committee (Approval No. 259/14).

### Clinical characterization of the study population

Patients were characterized by age, gender, CD4 cell count, HIV viral load and ART regimen. In addition, PLWH were classified according to the Center for Disease Control and Prevention (CDC) guidelines in CDC state A to C based on clinical criteria and CD4 T-lymphocyte counts.[24] Risk factors for anal carcinomas, such as smoking and sexually transmitted infections, were evaluated. Premedical history (PMH) was documented regarding diseases of the genito-anal region as well as chronic infectious and non-infectious complications, such as (anal) dysplasia and/or neoplasia and previous diagnostic procedures such as anoscopy or colonoscopy.

### AIN cytobrush screening and anal cytology by PAP smear assessment

The screening for AIN and/or anal carcinoma was performed based on the German-Austrian guidelines for anal carcinoma screening in PLWH.[19] Patients were only included if no documented receptive anal intercourse and clysters 48 occurred before the study-related cytobrush assessment. First, a clinical examination of the perianogenital area was performed. Clinical findings such as condylomata acuminata were recorded. AIN cytobrush screening was performed by inserting a cytobrush (*Jednorazowa Szczoteczka Typo Cyto*®, DAGA MED, Gdańsk, Poland) into the anal canal up to the *Linea dentata* 4 cm above the anus. Samples were collected by repeated clockwise rotation of the cytobrush with a slight pressure onto the mucosa. Cytobrush mucosa samples were processed accordingly to clinical routine diagnostic workup at the Institute of Pathology at Technical University of Munich, Munich, Germany. Anal smears were stained with Papanicolaou reagent and then evaluated by a PAP-trained pathology specialist. The diagnostic classification was performed according to the Munich Nomenclature II (Table 1).[25]

### Anoscopy

A board-certified specialist for proctology performed conventional diagnostic anoscopies. Clinical evaluation and mucosa biopsies from suspicious regions were performed upon staining

**Table 1** Histopathological classification of anal dysplasia

| | Munich nomenclature II | Munich nomenclature III | Bethesda classification | Histological correlation |
|---|---|---|---|---|
| Normal cell pattern with suspicious patient history | PAP II | PAP II | – | – |
| Mild dysplasia | PAP IIID | PAP IIID1 | LSIL | AIN 1 |
| Moderate dysplasia | PAP IIID | PAP IIID2 | HSIL | AIN 2 |
| Severe dysplasia | PAP IVa | PAP IVa-p | HSIL | AIN 3 |
| Carcinoma *in situ* | PAP IVa | PAP IVa-p | HSIL | AIN 3 |

of the suspicious areas with 3% acetic acid using a 4 mm skin biopsy punch (Stiefel Laboratorium AG, Offenbach, Germany).

### Statistical analysis

Statistical analysis was performed using Microsoft Excel 2013 (Microsoft, Redmond, WA, USA), SPSS Version 22.0 (IBM, New York, NY, USA). Descriptive statistics were measured by mean values, standard deviation, minimum and maximum. Categorical variables were measured in percentage (%) by absolute and relative frequencies. Statistically significant differences between two groups were tested by Student's *t*-test or Mann–Whitney *U*-test. Chi-squared test or Fisher's exact test was used to assess for independence as appropriate. A *P*-value ≤0.05 was considered to be statistically significant.

## Results

### Characteristics of the study population

In total, 101 PLWH, of which 84 were male and 17 female, were screened for anal dysplasia by PAP smear examination. Baseline characteristics could be found in Table 2. The mean age of the subjects at the time of examination was 50 years [standard deviation (SD): ±13.24 years]. 52% ($n$ = 53) of the subjects were MSM, 37% ($n$ = 37) were heterosexual and in 11% ($n$ = 11) no information on sexual preferences was available. 38% ($n$ = 38) reported current or prior smoking. 91% ($n$ = 92) received antiretroviral treatment, and 84% ($n$ = 85) had a HIV ribonucleic acid (RNA) load <40 copies/mL. According to the Centers for Disease Control and Prevention (CDC) classification for HIV, 50% ($n$ = 51) of the subjects had documented CDC state A, 20% ($n$ = 20) CDC state B and 30% ($n$ = 30) in CDC state C by the time the HIV infection was diagnosed. At the time of PAP smear examination, the majority of the patients (62%, $n$ = 63) had a CD4 cell count >500/µL. 35% ($n$ = 35) of subjects had a CD4 cell count between 200 and 499/µL. Only three subjects had a documented CD4 cell count <200/µL.

### Cytopathology results

According to the results from the cytobrush PAP smear examination, subjects were classified into three groups based on the Munich Nomenclature II: (group A: subjects with unremarkable PAP smear findings, group B: subjects with low- to middle-grade dysplasia of the anal mucosa and group C: subjects with high-grade dysplasia). Results are displayed in Table 2. Of all 101 subjects, 26.7% ($n$ = 27) had low-grade dysplasia and 9.9% ($n$ = 10) showed high-grade dysplasia. In line with the demographics of our cohort, in all three groups, higher male gender prevalence was found. The mean age of subjects with high-grade dysplasia was higher (60 vs. 50 years in group B and 48 years in group A). However,

**Table 2** Demographic and clinical characteristics of the study participants stratified according to the Munich II Papanicolaou smear classification

| Clinical classification | Group A<br>No dyplasia | | Group B<br>PAP IIID<br>AIN 1-2/LSIL | | Group C<br>PAP IVa<br>AIN 3/HSIL | |
|---|---|---|---|---|---|---|
| | Number<br>64 | %<br>64% | Number<br>27 | %<br>27% | Number<br>10 | %<br>10% |
| Male | **54** | 84% | **21** | 78% | **9** | 90% |
| Female | **10** | 16% | **6** | 22 | **1** | 10% |
| Tobacco smoking | **18** | 19% | **12** | 44% | **8** | 80% |
| Age (years) | **50** (25–80) + 12.79 | | **48** (29–79) + 13.47 | | **60** (46–78) + 10.84 | |
| CDC state A | **31** | 48% | **15** | 56% | **5** | 50% |
| CDC state B | **16** | 25% | **3** | 2% | **1** | 10% |
| CDC state C | **17** | 27% | **9** | 33% | **4** | 40% |
| CD4 cell count <200/µL | **1** | 1.5% | **2** | 7% | **0** | 0% |
| CD4 cell count 200–499/µL | **25** | 39% | **9** | 33.3% | **1** | 10% |
| CD4 cell count >500/µL | **38** | 59.3% | **16** | 59.2% | **9** | 90% |
| HBV infection | **19** | 29.6% | **9** | 33.3% | **5** | 50% |
| HCV infection | **0** | 0% | **3** | 11.1% | **1** | 10% |
| Positive syphilis serology | **16** | 25% | **12** | 44.4% | **3** | 30% |
| Chlamydia trachomatis | **3** | 4.6% | **3** | 11.1% | **0** | 0% |
| Condylomata acuminata | **8** | 12.5% | **4** | 14.8% | **4** | 40% |
| On ART | **60** | 93.7% | **24** | 88.8% | **9** | 90% |
| No ART | **4** | 6.2% | **3** | 11.1% | **1** | 10% |
| HIV RNA <40 cps/mL | **56** | 87.5% | **21** | 77.7% | **9** | 90% |
| HIV RNA >40 cps/mL | **8** | 12.5% | **6** | 22.2% | **1** | 10% |

neither the trend for age nor gender reached significance in our study.

### Association with immune status

Patients from all three groups were classified according to the CDC state classification. Most subjects had documented CDC state A and were under suppressive ART, achieving long-term suppression of HIV load. Our study did not show significant association between abnormal screening results and CDC classification, nor CD4 cell count, nor HIV viral load, respectively. Noteworthy, in the group with high-grade dysplasia 90% of the patients had a CD4 cell count over 500/μL, compared to group A and group B with 59.3% and 59.2%, respectively.

### Association with smoking

Over a third of patients in our study were smokers ($n = 38$). Smoking was significantly associated with mild to high level of dysplasia ($P = 0.001$).

### Association with chronic viral infections and sexually transmitted diseases

As chronic HPV infections in particular with multiple and high-risk HPV represent a risk factor for AIN and anal carcinoma, subjects were clinically examined for signs of an HPV infection such as condylomata acuminata.[26–29] Anal condyloma was significantly associated with abnormal screening results ($P = 0.045$). In group C, 40% of subjects suffered from condylomata acuminata vs. 12.5% in group A and 14.8% in group B. We also analysed the association between hepatitis B (HBV) and C (HCV) infection and abnormal screening results. While HBV and HCV were more common in group B and group C, these results did not reach significance in our cohort. Regarding STIs, our study did not find a significant association between chlamydia infection and PAP results. However, 12.8% ($n = 13$) of subjects were diagnosed with an active syphilis infection and 17.8% ($n = 18$) had a previous syphilis infection. Positive syphilis serology, including both active syphilis infection and previous syphilis infection, was significantly associated with abnormal screening result ($P = 0.016$).

### Follow-up examinations

Repeated cytobrush examinations for anal dysplasia were recommended to all subjects with an abnormal PAP smear finding. However, not all subjects took part in a follow-up assessment ($n = 22$). Follow-up examinations showed that results improved for 11 subjects, while eight subjects had documented persistent dysplasia. Three subjects progressed from PAP II to PAP IIID, and no patient progressed from PAP III to PAP IVa. Nineteen out of the 37 subjects with abnormal screening results underwent an anoscopy, and five subjects had a performed biopsy. Histology confirmed malignancy in two cases, one Buschke-Löwenstein tumour and one Keratoacanthoma.

## Discussion

The aim of this study was to evaluate the use of cytobrush examinations as screening tool for anal carcinoma in a HIV outpatient clinic. In our cohort, 37% subjects showed abnormal anal cytology. Compared to the literature, these numbers are low.[8] We assume that this observation is related to the good access to medical care, resulting in early diagnosis of HIV and HPV infection, easy access to antiretroviral therapy and better adherence to therapy.[30,31] Our cohort also includes both genders regardless of sexual orientation while previous studies often concentrated on MSM only. In Europe, men make up the majority of PLWH with women accounting for about a third of new diagnosis of HIV.[19,32] In total, 17% of our subjects were female and seven female subjects showed mild to severe dysplasia in their screening assessment. As an increased risk of HPV-mediated cervical and anal carcinoma in female PLWH has been reported, our result emphasizes that screening strategies for AIN should not neglect female PLWH.[14,33,34] Unfortunately, our study did not include enough female PLWH to investigate risk factors specific to this patient group. However, we hope our results encourage multicentre studies to address these questions. Similar to previous studies, we noticed that encouraging patients to participate in regular screening examinations is challenging. While improved screening strategies are essential for successful AIN prevention, patient compliance is equally important. Therefore, further efforts should be made to increase both male and female PLWH participation to AIN screening.

The second aim of our study was to investigate risk factor for anal dysplasia in PLWH. In line with previous studies, smoking increased the risk for low- to high-level AIN significantly ($P = 0.001$) in our cohort.[15,17] The increased incidence of cardiovascular diseases in PLWH has been clearly demonstrated.[2,3] As smoking is also a considerable risk factor for cardiovascular problems, preventive strategies for PLWH should include programmes to quit smoking. This illustrates that the management of PLWH requires multidisciplinary approaches.

Human papillomavirus infection is a well-known risk factor for AIN.[10] The majority of anal carcinomas are associated with the presence of HPV.[35] As in the routine clinical setting, we did not screen swabs for HPV DNA. However, we examined patients for condylomata acuminata.[36] Anal condyloma is considered a risk factor for AIN and anal carcinoma. Condyloma was used in this study as a clinical surrogate marker for HPV infection. There is increasing evidence for HPV vaccination as a prevention strategy in PLWH.[37–40] So far, HPV vaccination has only been recommended for girls aged 9–14 since 2006 and for boys aged 9–14 since 2018 in Germany.[41] For this reason, none of our subjects have been routine-vaccinated against HPV. The incidence of condylomata acuminata among PLWH in our cohort and the positive correlation with abnormal cytology suggest that novel

prevention strategies for HPV infection, such as vaccination, need to be further evaluated.[37–40]

One subject in our study belongs to the rare group of so-called elite controllers. Only about 0.15% of PLWH are elite controllers and manage to suppress HIV RNA without ART. Interestingly, this particular subject never showed an abnormal screening result. While this is a mere observation with no statistical significance, it raises the interesting immunological question if elite controllers are also able to 'control' HPV infection, thus lowering their risk for anal dysplasia.

In contrast to other studies, we did not see a significant association between chlamydia infection and abnormal screening result.[42] We believe that this is most likely due to the low incidence of chlamydia infections in our study cohort ($n = 3$). Interestingly, we discovered a significant correlation between positive syphilis serology and pathological PAP screening results ($P = 0.016$). On the one hand, reactive syphilis serology can be considered an indicator for sexual risk behaviour. On the other hand, it is tempting to speculate about the molecular pathomechanisms underlying this observation. Syphilis infection causes temporary damage to the anal mucosa, which could facilitate HPV transmission and eventually AIN development.[6,11] However, further studies will be necessary to investigate these research questions. Synergistic effects between different STIs for the development of high-grade anal dysplasia have been described before; however, our study could confirm this observation in the setting of an outpatient clinic.[42] Recurrent syphilis infection in PLWH can be interpreted as an indicator of altered sexual risk behaviour. Recently, the increased use of pre-exposure prophylaxis for HIV has raised concerns about greater risk behaviour among MSM and the possibility that this causes a higher incidence in STIs or HPV-mediated malignancies.[43–45] The positive correlation between syphilis, HPV infection and AIN highlights the importance of regular STD screening in PLWH and the benefit of promoting safe sex education.

Expert guidelines recommend the performance of HRA in patients with high-risk lesions.[22,46] Since at the time of this study HRA was not an established and validated procedure for screening of anal carcinoma at our centre, we decided to perform the examination by conventional anoscopy.[47,48] Not all abnormal screening results could be confirmed by anoscopy in our cohort. This has been observed in other studies as well.[49] Perhaps cytobrush examinations in risk groups could be combined with syphilis serology, HRA and HPV screening for high-risk viruses to increase the sensitivity of anal carcinoma screening.[50–52] Unfortunately, our study cohort was not large enough to evaluate this question.

Taken together, our study investigated the use of cytobrush examination for the screening of anal carcinoma in an outpatient clinic with male and female PLWH. We confirmed the significant association between smoking and anal dysplasia in our cohort. Additionally, we could demonstrate that STIs, such as condyloma acuminata and syphilis, are significantly associated with an abnormal histology results in PLWH.

Based on our results and current studies, we reached the conclusion that regular PAP tests along with clinical examination and HRA should be a part of the yearly screening for anal carcinoma in PLWH. In our study, we only had limited follow-up data for PAP examinations to evaluate. This is mainly due to low attendance of follow-up appointments. Since HPV infection is one of the most common sexually transmitted diseases and a substantial risk factor for various carcinomas among others cervical and anal carcinoma, we consider HPV and anal dysplasia screening in PLWH an essential approach for the prevention of anal carcinoma. Ideally, medical insurance companies should support screening strategies for anal carcinoma in PLWH, as the lack of reimbursement makes it difficult for clinicians to establish screening tools in their daily practice. Moreover, we suggest that HPV vaccination especially for MSM and PLWH with high-risk behaviour should be a part of future prevention strategies.[37–40,53–55] While improved screening strategies are essential for successful AIN prevention programmes, patient participation is equally important.[56] For this reason, further efforts should be made to encourage both male and female PLWH to take part in screening and prevention programmes.

## Acknowledgements

The authors would like to thank Alexander Konstantinow, M.D., Josef Keller, M.D., and Johannes Schimmler, M.D., for performing the proctoscopic examination and Gregor Weirich, M.D., for assistance with cytopathology.

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