

# Quality of life in women with HPV and accuracy of direct visual anal inspection with acetic acid and lugol compared to high-resolution anoscopy to diagnose intraepithelial anal lesion

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## Abstract

*Objectives: to describe life quality of women with HPV and analyze the accuracy of anal visual inspection with acetic acid and lugol compared to high-resolution anoscopy in the detection of anal intraepithelial lesions.*

*Methods: diagnostic evaluation study conducted with adult solid-organ transplant recipients and/or diagnosed with HIV and/or with a history of anogenital neoplasia, attended at the High Resolution Anoscopy outpatient clinic between April and December 2018. To calculate the accuracy parameters, 87 women participated: 44 with lesions and 43 without them. The 44 women with lesions were also subjected to a descriptive study to assess their life quality using the SF-36 questionnaire.*

*Results: it was observed that almost half of the women in the study practiced vaginal, anal and oral intercourse without condom. History of HPV infection and anogenital neoplasia were the most prevailing with percentages of 81% and 72.7%, respectively. In five out of the eight domains of SF-36 they did not perform well in regard to life quality. Visual inspection with acetic acid and lugol presented sensitivity of 22.7% and specificity of 100%.*

*Conclusion: unsatisfactory life quality was evidenced. Direct visual inspection with acetic acid and lugol should not be used in trials to spot intraepithelial HPV lesions, for it presents low sensitivity.*

**Key words** *Papillomavirus infections, Screening, Anus neoplasms, Quality of life*



## Introduction

The human papilloma virus (HPV) is the most frequent infectious agent of the world.<sup>1,2</sup> In 2012, approximately 4.5% (640,000) new cancer cases were attributed to HPV infection.<sup>3</sup> Anal cancer is strongly associated with HPV infection.<sup>4</sup> Within the general public, anal cancer is relatively uncommon, representing 3% of all gastrointestinal tract cancers. However, the cases are increasing globally having almost doubled in the last 25 years.<sup>5</sup>

Similar to cervical cancer, anal cancer is preceded by a high-grade intraepithelial anal neoplasia, a pre-malignant lesion caused by the presence of HPV, which can evolve into squamous cell carcinoma of the anal canal. The behaviour of the mentioned lesions, as well as the most appropriate methods of tracking and observing them, remain controversial.<sup>6</sup> Most strategies utilized nowadays to prevent and treat anal lesions related to HPV are based on the understanding of how HPV infections in the cervix work and on the evolution of intraepithelial lesions and cervical cancer.<sup>7</sup>

The tracking triad – anal cytology, high-resolution anoscopy (HRA) and biopsy – remains controversial when it comes to the anal canal. Anal cytology, although of its low-cost and being easy to perform, does not have ideal accuracy, particularly in high risk populations with indication of surveillance.<sup>8</sup> HRA was introduced as complementary to cytology, aiming to increase sensibility and specificity in the detection of lesions precursors of anal cancer.<sup>9</sup> However, to this date, its impact as a tracking modality remains inconclusive. The efficiency of HRA is only evident when associated with other tracking methods. Another limitation of this modality is the necessity of training, with the learning curve being around 200 exams.<sup>10</sup>

In some African countries and rural areas of China - places with high incidence of cervical cancer -, there is great difficulty in accessing trained professionals to perform tracking exams by means of colposcopy. Consequently, the World Health Organization (WHO) recommended the use of direct visual inspection with acetic acid (VIA) and lugol's iodine (VILI) as alternative methods of triage and subsequent forwarding to colposcopy.<sup>11</sup> Considering the well documented relationship between HPV and cervical and anal cancer, the difficulties in training professionals to perform HRA and its limited offering by medical centers of high complexity, the method VIA/VILI could become an option in the tracking of high-grade anal intraepithelial lesions.

Within other aspects to be considered in the

adequate prevention, diagnosis and treatment of HPV, the quantitative measures of life quality could serve as an indicator to guide strategies for intervention and therapeutic planning as well as creating parameters to define actions to promote public health. There are few studies which evaluate the impact of lesions caused by anal HPV in women's quality of life.<sup>12,13</sup> Taking into consideration the circumstances, the goal of this paper is to analyze the accuracy of VIA/VILI compared to HRA to detect intraepithelial anal neoplasia (IAN) and describe the profile and quality of life of women with anal HPV.

## Methods

This is a descriptive cross-sectional observational study and diagnostic evaluation, performed between April 2018 and December 2018. The population in the study is constituted by women that attended the HRA outpatient clinic of the Institute of Integrative Medicine Prof. Fernando Figueira (IMIP – Portuguese acronym) in accordance to the following criteria of eligibility: 18 years of age or more, HIV positive and/or having undergone solid-organ transplantation (liver, kidney and heart) and/or with a history of anogenital neoplasia and/or HPV infection. Pregnant patients were not included. In this sense, a non-probabilistic sample of 87 women was obtained.

To calculate the analysis of the accuracy parameters of VIA/VILI compared to HRA to detect LIA, all 87 women participated in the study: 44 with LIA and 43 without it.

All of them responded to a questionnaire that included variables such as sociodemographic, socioeconomic, clinic and the sexual life that preceded the performance of the direct visualization exam with VIA/VILI and HRA. The phases of the exams included checking of skin and mucosa conditions and inspection of the perianal region post-application of VIA with direct visualization followed by HRA exams; conventional anoscopy after VIA application in the anal canal region with direct visualization followed by HRA performance. The procedures were performed on the same patients, at the same time, by the same professional trained to perform those exams.

The LIA under direct visualization, was considered positive if two conditions were fulfilled: (1) the presence of well delimited acetowhite areas in the perianal region or in the anal canal, close to one minute after the direct application of the diluted solution of acetic acid 5% - VIA (the acetowhiteness effect occurs gradually in the next minute and can

disappear after that time. Therefore it is possible to repeat the VIA application every 2 or 3 minutes during the exam); (2) the absence of fixation or a very subtle one in the anal canal mucosa about one minute after the application of a lugol 5% solution. In general, a high degree of LIA absorbs less iodine, displaying colors that vary between mustard yellow and saffron yellow. LIA performed by means of HRA was considered positive if the conditions mentioned above were present.

The studied variables were: race/self-declared color; age; stable relationship, origin, education and socioeconomic status. To measure the socioeconomic status, "Brazilian Criteria of Economic Classification" (CCEB – Portuguese acronym) was used, built on scores related to the possession of goods and level of schooling of the head of family. The score varies from 0 to 46 and the higher the better the economic situation of the subject is. According to that criterion, eight economic categories are formed: A1, A2, B1, B2, C1, C2, D e E. The individuals with the best situation are located on A1, and the worst in E.<sup>14</sup>

The variables related to sexual life were: first time, sexual orientation, frequency of sexual activities in the last six months, sexual practices, the use or non-use of condom, number of partners in the last 6 months and history of STDs. The clinical variables were: base diagnosis, use of regular medicine in the last six months, habits and other diseases such as: Systemic arterial hypertension, dyslipidemia and mellitus diabetes. The variables on habits were based on the definitions adopted by Vigitel Brasil (2013).<sup>15</sup> Independently of frequency, every woman that smoked was considered a regular smoker. Drinking four or more doses of alcohol at the same occasion was considered abusive.

The data related to the direct visualization exam VIA/VILI and HRA was filled in the appropriate questionnaire by the performing professional. All other questions were read to the participants and the answers were listed in a specific form. To avoid embarrassment and grant confidentiality, this process was held in a private and reserved environment.

In the 44 women with LIA, a descriptive study was also performed, with the use of a questionnaire about their quality of life. For the variable related to quality of life, in general, "The Medical Outcomes Study 36 – item Short form Health Survey" (SF-36) was used, 16,17 a generic tool to evaluate life quality levels, in Brazil, not being specific to any age, sickness or treatment. The current SF-36 is multidimensional, composed by 36 questions that involve eight

domains: physical functioning, physical role limitations, pain, general health perceptions, vitality, social functioning, emotional role limitation, mental health, and one more question that demand a comparison between the actual health conditions and conditions from the year before. The final score varies from 0 to 100. Zero being the worst, 100 being the best health condition in each one of the evaluated domains.

The data was typed twice, processed and analyzed with the help of the SPSS 13.0 program. Inconsistencies were detected and corrected by means of consultation and questionnaires. Relative and absolute frequency of nominal and ordinal variables, the mean standard deviation and variance were calculated. Since the SF-36 scores were, almost entirely, not presenting a normal distribution, evaluated by the Kolmogorov-Smornov and Shapiro-Wilko tests, the presentation of average values was chosen. To rate the accuracy of the direct inspection of the perianal and anal canal with VIA/VILI compared to HRA to diagnose LIA, the calculation of sensitivity, specificity, predictable values and negative likelihood ratio and its confidence intervals. This study was registered by the Human Research Ethics Committee of IMIP, under the series number CAAE 73677517.30005201, and the report number 2.349.114e was duly approved in October 25, 2017. All women were invited to the study and were included in the case that they agreed voluntarily to participate, signing the free consent form ("*Termo de Consentimento livre e Esclarecido*").

## Results

The women's identification and socioeconomic data are described in Table 1. The average age was 42 years old, with the youngest being 24 and the oldest 79. 75% (33) were black, 77.3% (34) urban and 72.7% (32) were in a stable relationship. Of the 44 patients, 25% (11) were illiterate or had a very low level of literacy, and only 39.5% had finished high school and/or started college. Most of them (90.7%) came from a low social stratum (classes C, D and E, according to "Brazil Criterion"). Among sexual life practices (Table 2), it was verified that they began to be sexually active when 18, in average; 100% of them declared to be heterosexual, half of them had intercourse some times a week, 72.7% (32) had only one sexual partner, 47.7% (21) practiced vaginal, anal and oral intercourse and in 47.7% (21) of the cases they did not use protection. As for their clinical features (Table 3), 81% (31) had had HPV infection and 72.7% (32) anogenital neoplasia. In

relation to habits and comorbidity: smoking was declared in 4.5% (2), alcohol abuse in 9.1% (4), arterial hypertension in 27.3% (12), hyperlipidemia in 18.2 % (8) of the cases, however, there was not any diabetes mellitus diagnosis.

The accuracy of the perianal and anal canal direct visualization with the use of VIA and VILI, compared with HRA to diagnose intraepithelial anal lesion is described in Table 4. VIA/VILI presented sensibility of 22.7% (CI95% 12.0-36.8) and specificity of 100% (CI95% 93.3 – 100.0).

Figure 1 summarizes the score results on quality of life, within each domain evaluated by the questionnaire SF-36. Five from the eight domains included in the SF-36 – Social functioning, Pain, Mental health, General health perceptions and Vitality – did not present good performance in relation to quality of life. The average of the scores were 75, 72, 72, 67 and 65, respectively

## Discussion

The women's profile showed social vulnerability characterized by low level of education and low purchasing power, predominantly in people of color. Similar results were found in a study of anal HPV

prevalence involving 152 women having pre-malignant lesion or cervical and anal cancer simultaneously in which it was observed that most women were not white (67.1%) and had familiar income inferior to the minimum wage. Those socioeconomic characteristics depict the profile of users of Brazilian Health Care System.<sup>18</sup>

Another apparent aspect was the age of the first sexual experience, which was a little higher than the average indicated in the medical literature. An epidemiologic study on the sexual behavior of Brazilians done by the Ministry of Health in 2006,<sup>19</sup> found that the mean age that Brazilian women had their first intercourse was 15. In another one, most women (88.7%) began their sexual life before their 20's (and 41.7% of them even before their 16's).<sup>18</sup> This precocious beginning of sexual life might be associated with a higher number of partners and therefore a longer exposure to HPV, increasing the chances for more oncogenic subtypes of HPV and a higher degree of vulnerability to cervical cancer.

Besides the precocious first intercourse, other risk factors are: smoking, anal sex, having more than two sexual partners throughout one's life and chronic immunosuppression.<sup>20</sup>

It was observed that only 13.6% of patients in

**Table 1**

Socioeconomic identification data of women with intraepithelial anal lesion. Recife, 2018.

Variables	N=44*	%
Race/color (self-reported)		
Brown	18	40.9
Black	15	34.1
White	8	18.2
Others	3	6.8
Age		
Minimum	24	
Maximum	79	
Average ± standard deviation	43.82 ± 13.04	
Median	42	
Origin		
Urban	34	77.3
Rural	10	22.1
Stable relationship		
Yes	32	72.7
No	12	27.3
Education Level		
Illiterate to elementary school	11	25.6
Elementary school to incomplete High School	15	34.9
High School to College (not necessarily complete)	17	39.5

continue

\*When the total does not match, there was loss of information from the variable.

**Table 1** **concluded**

Socioeconomic identification data of women with intraepithelial anal lesion. Recife, 2018.

Variables	N=44*	%
Socioeconomic Stract (Brazil Criterion)		
A	-	-
B1	1	2.3
B2	3	7.0
C1	6	14.0
C2	21	48.8
D and E	12	27.9

\*When the total does not match, there was loss of information from the variable.

**Table 2**

Sexual life features of women with intraepithelia na lesions. Recife, 2018.

Variables	N=44*	%
Begining of sexual life (complete years)		
Minimum	14	
Maximum	30	
Average ± pattern deviation	18.68 ± 3.65	
Average	18	
Sexual Sexual orientation		
Heterossexual	44	100.0
Homossexual	-	-
Frequency of sexual intercourse in the last six months		
Daily	5	13.2
A few times a week	19	50.0
A few times a month	13	34.2
Not once	1	2.6
Sexual activities		
All	21	47.7
Vaginal	11	25.0
Anal and vaginal	8	18.2
Oral e vaginal	3	6.8
Anal e oral	1	2.3
Number of partners in the last six months		
1	32	72.7
2 or more	4	9.1
None	8	18.2
Use of protection		
Always	9	20.5
Sometimes	8	18.2
Rarely	6	13.6
Never	21	47.7
History of STDs		
HPV	34	81.0
Syphilis	1	2.4
No	7	16.6

\*When the total does not match, there was a loss of information from the variable.

**Table 3**

Clinical features of women with anal intraepithelial lesion. Recife, 2018.

Variables	N=44*	%
<b>Basis diagnosis</b>		
HIV/Aids	6	13.4
Transplant	6	13.6
History of anogenital neoplasia	32	72.7
<b>Regular use of medicines in the last six months</b>		
Corticosteroid	1	2.3
Immunosuppressant	5	11.6
Antiretroviral	6	14.0
Does not use	31	72.1
<b>Habits (current)</b>		
Alcohol abuse	4	9.1
Smoking	2	4.5
<b>Comorbidities (referred to by a doctor)</b>		
Hypertension	12	27.3
Diabetes mellitus	-	-
Hyperlipidemia	8	18.2

\*When the total does not match, there was loss of information from the variable.

**Table 4**

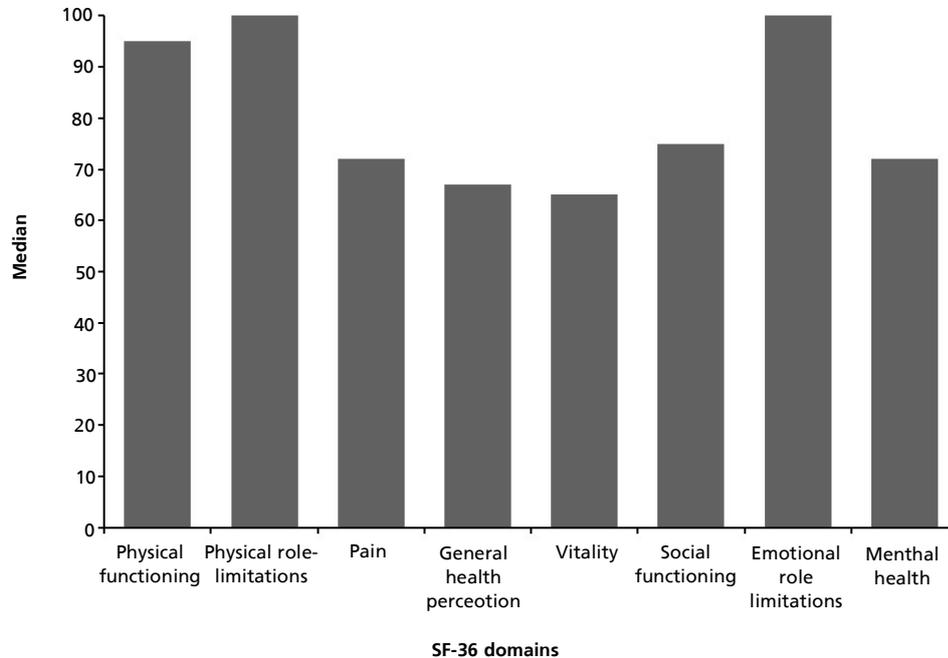
Parameters of accuracy of direct anal visualization with acetic acid use and lugol solution compared to high-resolution anoscopy of women with anal intraepithelial lesion. Recife, 2018.

Exam	Presence of perianal or anal canal lesion by high resolution anoscopy			Accuracy	Sensitivity (CI95%)	Specificity (CI95%)	PPV (CI95%)	NPV (CI95%)	NLR (CI95%)
	Yes	No	Total						
Presence of perianal or anal canal lesion by direct visualization				60.9	22.7 (12-36.8)	100.0 (93.3-100.0)	100.0 (74.1-100.0)	55.8 (44.6-66.6)	0.8 (0.0-0.95)
Yes	10	-	10						
No	34	43	77						
Total	44	43	87						

CI = Confidence Interval; PPV = Positive Predictive Value; NPV = Negative Predictive Value; NLR = Negative Likelihood Ratio. Note: The division by zero did not allow the calculation of the Positive Likelihood Ratio.

Figure 1

Median scores of SF-36 domains of women with intraepithelial anal lesion. Recife, 2018.



the study were smokers. Two other authors who wrote on women with HPV lesions related a smoking occurrence between 21.1% and 40.4%, which is a little more elevated rate compared to the data found in this sample.<sup>21,9</sup> This finding can reflect on the positive effect of Programa Nacional de Controle ao Tabagismo (a national political program to reduce and control smoking) initiated in 1985 by Brazilian Ministry of Health.

In reference to sexual practices, almost half the women in the study (47.7%) were adherent to vaginal, anal and oral intercourse and never used protection. HPV was the prevalent STD infection, figuring 81% of the sample. The literature showed to be contradictory to these results. A study published in 2009 observed that the greater number of women (82.5%) denied practising anal sex.<sup>21</sup> In relation to the number of partners, 33.3% of these women had 2 to 3 sexual partners and 66.7% did not report the regular use of barrier methods. Most of them (82.5%) denied a past of other transmissible sexual diseases besides HPV.<sup>21</sup> Another study realized in 2019 showed a higher number of partners and a wider adherence to anal sex practice among the subjects. Around 79.8% of them had up to 5 partners,

51.5% had anal coitus and only 23.4% used condoms.<sup>18</sup> These contradictory findings might be explained by gradual change of social behavior in women.

Still about sexual practice, a study realized with women who presented Immunodeficiency caused by HIV showed that the passive receptive sex with at least one partner is a risk factor for anal HPV infection.<sup>22</sup> Aproximately 56% of the women in this study reported practicing anal sex. The prevalence of a high-risk LIA in the anal region among the subjects was of 27%. Women that reported this type of sex with more partners throughout their lives presented higher incidence of high-risk lesions than the ones who have had one or no partners at all: 34%, 28% and 17%, respectively.<sup>22</sup>

Evidences suggest that cervical infections caused by high-risk HPV and cervical cancer diagnosis are the most important determining factors for a woman with a high-risk profile to get anal cancer.<sup>23</sup> However, although the high-risk types of HPV are necessary causes to cervical cancer, additional genetic events are essential for malignanzation in most carcinomas, anal or in other areas.<sup>21</sup> These findings suggest that there is an association between

anal receptive coitus, persistent HPV infection and number of sexual partners.

In the present paper, the aim is to evaluate the accuracy of direct visual inspection using VIA/VILI in HPV infected women. This strategy is suggested by the WHO for countries with limited resources and few professionals trained to perform colposcopies with the advantages of having a lower cost, easier training for professionals, and no need for specialized equipment to perform.<sup>11</sup>

Large amounts of studies that analyze the accuracy of direct visual inspection using VIA/VILI in women with HPV exist. However, all of them were in the uterus cervix. Carrying out a meta-analysis on the accuracy of visual inspection with acetic acid and with lugol iodine to track cervical cancer, a 80.6% sensibility of VIA and a 92.4% of VILI to high risk lesions was verified.<sup>24</sup>

The same pattern was not observed when evaluating the accuracy of direct visualization with VIA/VILI on perianal and anal regions. The sensibility found in the current study was low and the specificity was high, revealing it not to be a good method of screening in patients with anal HPV lesions.

This study observed limitations in accuracy. Our sample was previously selected and composed of women who had had confirmed HPV lesions in other places and with indication of HRA by an abnormal Pap test, therefore it is possible that the VIA/VILI correlation of sensibility, as well as specificity had been overestimated. The study's strong points include the size of the sample, the application of a complete clinical questionnaire and the fact that the exam was performed by a trained professional, with methodological rigor. Besides, due to the high specificity found, the patients with positive exam results might initiate treatment for the found lesions, by virtue of the occurrence of false positive results being insignificant.

Concerning the impact on life quality of an infected HPV patient and the presence of NIA in patients from the studied sample, it was observed that five SF-36 domains did not present satisfactory performance. The domain Vitality, which measures energy and fatigue in patients, showed the lowest scores in comparison to other domains. The second worst score was "General health perceptions", which evaluates how a patient feels towards the global state of health, showed equally low scores. The domain "Social functioning", the fifth in the rank, showed results a little more elevated, however, still related to the worsening of patient's quality of life.

The design of this study did not allow us to

clarify a causal link between life quality and HPV lesion presence, since it was impossible to establish a time sequence between the two. A prospective cohort analyzed the psychological impact on patients' life quality when they were informed about the tracking exams abnormality in the reference center to prevent anal cancer in Australia.<sup>25</sup> This aforementioned study included as subjects male bisexuals and other men who had sex with males, particularly HIV positives aged 35 or more. The subjects filled a form on global state of health, psychological aspects of their lives at the first consultation and repeated the same questionnaire 2 weeks and 3 months later. After getting the results of the tracking exams, patients that were positive showed significantly lower scores when compared to patients that tested negative, mainly when it came to intrusive thoughts and fear of developing cancer.<sup>25</sup>

Another study observed life quality in 118 patients of both genders who had anogenital warts using SF-36 and 2 others questionnaires: Skindex-29 and GHO-12.<sup>26</sup> A significant association between the disease quantified by size (>200mm<sup>2</sup>), the number of anogenital lesions and the lowering of all scores in SF-36 below the average, signifying a worse state of global health, was observed. Therefore, even though not being considered a serious medical condition, HPV lesions might compromise patients' quality of life greatly.

Although gender differences might jeopardize the results comparison, studies on women's quality of life when infected with HPV are still scarce.<sup>26</sup>

Thus, the direct inspection with VIA/VILI in the perianal and anal regions did not reproduce the same performance as VIA/LILI in the cervix, for it presents low sensibility and, therefore, must not be used as a screening tool to LIA. However, as a method of high specificity, it might be used to locate lesions that need treatment in locations with fewer resources, because of its wide availability, low cost and it's precision. Subjects in this study had an unsatisfactory quality of life, although the study design did not allow us to establish a causality link between the two facts. Further studies with a more adequate local design to deepen the investigation are necessary.

### Authors' contribution

Marinho GA: conception and structuring of the project, sampling, tabbing and data analysis, writing, critical review of intellectual content final approval of the version submitted to publishing. Oliveira MG: conception and structuring of the project, sampling,

tabbing and data analysis, writing. Silveira RK: conception and structuring of the project, sampling, tabbing and data analysis, writing, critical review and review of intellectual content. Silva ACCC: data collection, writing, critical and intellectual review. Melo Filho DA: tabbing and data analysis and interpretation. Heraclio AS: project structuring, critical review of intellectual content and approval of final version.

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