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## Review Article

# Screening anal cancer in women living with HIV/AIDS



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### ABSTRACT

**Aim:** Addressing the main methodologies published in the scientific literature and used to screen anal cancer in women living with HIV/AIDS.

**Methodology:** The current study is an integrative literature review applied to articles published between 2013 and 2017 in databases such as PUBMED, EBSCO and LILACS.

**Results:** Eight studies were selected to compose the current review after the inclusion and exclusion criteria were applied. All the articles had evidence level IV. Anal cytology and the DNA-HPV test were the methodologies prevailing in the studies. The number of participants in the studies ranged from 35 to 863, and all the studies involved women living with HIV/AIDS. The aim of most of the herein reviewed studies was to assess the prevalence of anal cytologic changes or HPV infection in women living with HIV/AIDS (WLHA).

**Conclusion:** Studies have pointed out that there is concern about high anal cancer and anal HPV infection rates. They also highlighted the importance of the screening procedure for anal cancer prevention through cytology associated, or not, with molecular HPV detection methods.

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## Rastreamento do câncer anal em mulheres vivendo com HIV/AIDS

### RESUMO

**Objetivo:** Abordar as principais metodologias que podem ser utilizadas para o rastreamento do câncer anal em mulheres vivendo com HIV/AIDS, que têm sido publicadas atualmente na literatura científica.

**Metodologia:** Trata-se de uma revisão integrativa de literatura, realizada através de pesquisa de artigos nas bases de dados PUBMED, EBSCO e LILACS, publicados entre os anos de 2013 a 2017.

#### Palavras-chave:

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Câncer anal

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**Resultados:** A partir da aplicação dos critérios de inclusão e exclusão, foram selecionados oito estudos para compor essa revisão. Todos possuíam nível de evidência IV. As metodologias que predominaram nos estudos foram a citologia anal e o teste DNA-HPV. O número de participantes nos estudos variou de 35 até 863, e todos envolveram mulheres vivendo com HIV/AIDS. A maioria tinha o objetivo de avaliar a prevalência de alterações citológicas anais ou infecção pelo HPV em mulheres vivendo com HIV/AIDS.

**Conclusão:** Os estudos apontaram que há uma preocupação com os altos índices de câncer anal e infecção anal por HPV. Também registram a importância do rastreamento para prevenção do câncer anal, através da citologia associada ou não a métodos moleculares de detecção do HPV.

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## Introduction

Anal cancer development is associated with human papillomavirus (HPV) infection.<sup>1</sup> The advancement in the antiretroviral therapy (ART) enables women living with human immunodeficiency virus (HIV) or with acquired immunodeficiency syndrome (AIDS) to increase their life expectancy. However, it raises their risk of developing comorbidities such as anal cancer.<sup>2,3</sup>

HIV/HPV coinfection in WLHA is a risk factor for the development of such neoplasm, mainly because of the immunocompromised condition faced by these patients.<sup>4</sup> In addition, WLHA are at increased risk of infections caused by more than one HPV type, mainly those of high oncogenic risk such as 16 and 18.<sup>3,5</sup> It is estimated that 70% of anal cancer cases are HPV-dependent, since the infection persistence predisposes patients to develop the disease.<sup>2,4</sup>

The overall incidence of anal cancer is low; however, this incidence has been increasing in WLHA,<sup>5,6</sup> whose risk of developing the disease is 5 to 14 times higher than that of women without HIV.<sup>7</sup> In addition, the prevalence of anal infections caused by HPV is higher in WLHA with history of cervical abnormalities.<sup>8</sup>

The anal cancer screening in some countries is conducted through cytological examination, which is followed by anoscopy and/or biopsy, whenever abnormalities are detected. Anal cytology may be performed similarly to that of the cervix, since the anus also has a transformation zone, which is vulnerable to HPV infection and lesion development.<sup>7</sup> The examination is performed through the conventional method, or liquid medium<sup>9</sup>; sample collection may be performed by scraping the anal canal with a brush, or Dacron swab, moistened in physiological solution, introduced 2–4 cm in the canal. The slides are processed through Papanicolaou technique and the results are classified according to the Bethesda System.<sup>10–12</sup>

Anoscopy is recommended when anal cytology shows abnormal results, since the exam identifies lesion sites to be treated and subjected to biopsy. The results need further confirmation through histopathological examination.<sup>3,4</sup> In addition, the use of the HPV test, both as virus detection method and as viral typing, at low or high oncogenic risk, has been constantly discussed as complementary to cytological screening.<sup>13</sup>

A screening program may be effective to this at-risk population, due to increase in the number of WLHA cases, since it would help detecting pre-neoplastic lesions and enable their treatment, thus reducing the incidence of anal cancer.<sup>14</sup> Therefore, the aim of the current study is to address the main methodologies available in the scientific literature, which may be used to screen anal cancer in WLHA.

## Methodology

The present study is an exploratory, descriptive and integrative literature review based on the search, assessment and synthesis of available evidences on the herein addressed subject. The research was conducted in March 2017. It comprised databases belonging to the US National Library of Medicine/National Institutes of Health (PUBMED), to the Latin-American and Caribbean System on Health Sciences Information (LILACS), and to the Elton B. Stephens Company (EBSCO). The following meshes were used in the search: “Anal cancer in HIV”; “Anal cancer cytology HIV”; and “Anal cancer screening HIV”. The meshes were crossed through the Boolean operator AND.

Studies conducted from 2013 to 2017, which addressed the prevalence of HPV infection in WLHA, and anal cancer screening methods applied to this population, were herein included. The period between 2013 and 2017 was selected to allow identifying studies on the subject conducted after the “Clinical Protocol and Therapeutic Guidelines for HIV Infection Management in Adult Individuals” was published by the Brazilian Ministry of Health in 2013. Studies conducted outside the pre-established period; those whose sample comprised men, men and women, and children; abstracts; studies with restricted access; in duplicate; reviews; treatment approaches; case reports; and studies addressing anal cancer not related to HPV infection were excluded from the current review. Next, the texts were read in full, the information were explored, data were extracted and the content was analyzed. Tables were prepared to categorize the results; they included data about the author, country where the study was carried out, publication year and evidence level in the study; study type; sample size and recruitment period; methodology; as well as the main anal cytology, anal HPV, anoscopy/biopsy and cervical cytology results (Tables 1 and 2).

**Table 1 – Characterization of selected articles according to publication data, study type, evidence level, sample size and methodology.**

Article	Author Place Year	Study type/evidence level	Sample size/recruitment period	Methodology
A1	Gaisa et al. USA 2016	Retrospective cohort study IV	745 WLHA 2009 to 2014	Conventional cytology (anal) Anoscopy
A2	Goeieman et al. South Africa 2017	Cross-sectional study IV	200 WLHA <sup>a</sup>	Conventional cytology (anal and cervical) Anoscopy DNA-HPV test: Digene Hybrid Capture 2 and Aptima E6/E7 mRNA to detect HPV
A3	Hessol et al. USA 2013	Nested cohort cross-sectional study IV	470 WLHA <sup>b</sup> 2001 to 2003	Liquid-based cytology (anal) Conventional cytology (cervical) Colposcopy and Anoscopy DNA-HPV test: PCR and hybridization typing
A4	Pittyanont et al. Thailand 2014	Prospective descriptive study IV	590 WLHA 2013 to 2014	Conventional cytology (anal) DNA-HPV test: Cervista human papillomavirus high risk (HPV HR) assays and Cervista HPV 16/18 assays
A5	Sananpanichkul et al. Thailand 2015	Prospective descriptive study IV	599 WLHA 2013 to 2014	Conventional cytology (anal and cervical)
A6	Bisherwal et al. India 2016	Cross-sectional study IV	40 WLHA <sup>a</sup> 2011 to 2013	Conventional cytology (anal and cervical)
A7	Cambou et al. Brazil 2015	Cohort study IV	863 WLHA 2011 to 2013	Liquid-based cytology (anal and cervical) Anal DNA-HPV test: PapilloCheck HPV-Screening Test Cervical DNA-HPV test: Linear-Array HPV Genotyping Test
A8	Heard et al. France 2015	Nested cohort cross-sectional study IV	171 WLHA 2012	Liquid-based cytology (anal and cervical) Anoscopy DNA-HPV test: Linear-Array HPV Genotyping Test

WLHA, women living with HIV/AIDS.

<sup>a</sup> The period when the study was conducted was not described.

<sup>b</sup> The study also included women without HIV, whose results were not included because they were not relevant to the aim of the integrative review.

## Results

The mesh-based search generated 881 studies in total; eight were selected according to the pre-established inclusion and exclusion criteria. Five out of the eight studies derived from PUBMED, three derived from EBSCO, and no study was selected from LILACS (Fig. 1).

Most of the studies (3 articles – 37.5%) were carried out in 2015, 2 (25%) were conducted in 2016, and only 1 (12.5%) study was performed in 2013, 2014 and 2017. All the studies had evidence level IV. The countries where they were carried out were Brazil, India, South Africa and France (1 study each); as well as Thailand and the United States (2 studies each).

The sample size in the studies varied from 35 to 863 WLHA; four different anal lesion screening methodologies were identified: three studies used anal cytology, anoscopy and DNA-HPV test; two used anal cytology associated with DNA-HPV test; two used anal cytology, only; and one study used anal cytology and anoscopy. Studies using conventional cytology prevailed (62.5%); they were followed by 2 (25%) studies that used the liquid-based method; and by 1 (12.5%) study that applied liquid-based cytology to the anal sample and conventional cytology to the cervical one. Liquid-based cytology

was the method of choice in most of the studies that performed the HPV-DNA test.

With respect to clinical follow-up, only half of the studies performed anoscopy when changes were found in the anal cytology, or colposcopy, when cervical changes were diagnosed.

The findings were distributed as follows, according to the overall change rates: 26.3% of WLHA whose anal cytology showed some atypia or lesion; 56.5% positivity in DNA-HPV tests; 49.5% underwent anoscopy and 53.7% of them had the anal cytology changes confirmed through histological examination.

## Discussion

Screening using anal cytology is the most cost-effective and easiest method, although data about its sensitivity and specificity in the literature remain scarce. One of the arguments in favor of this method lies on the biological similarity between cervix and anal specimens. In addition, the application of concomitant cytological screening to higher-risk patient groups may help decreasing the number of anal cancer cases.

Two cytological examination techniques were used in the herein reviewed studies. Conventional cytology was used in

**Table 2 – Synthesis of the results recorded in the articles selected according to the described methodologies.**

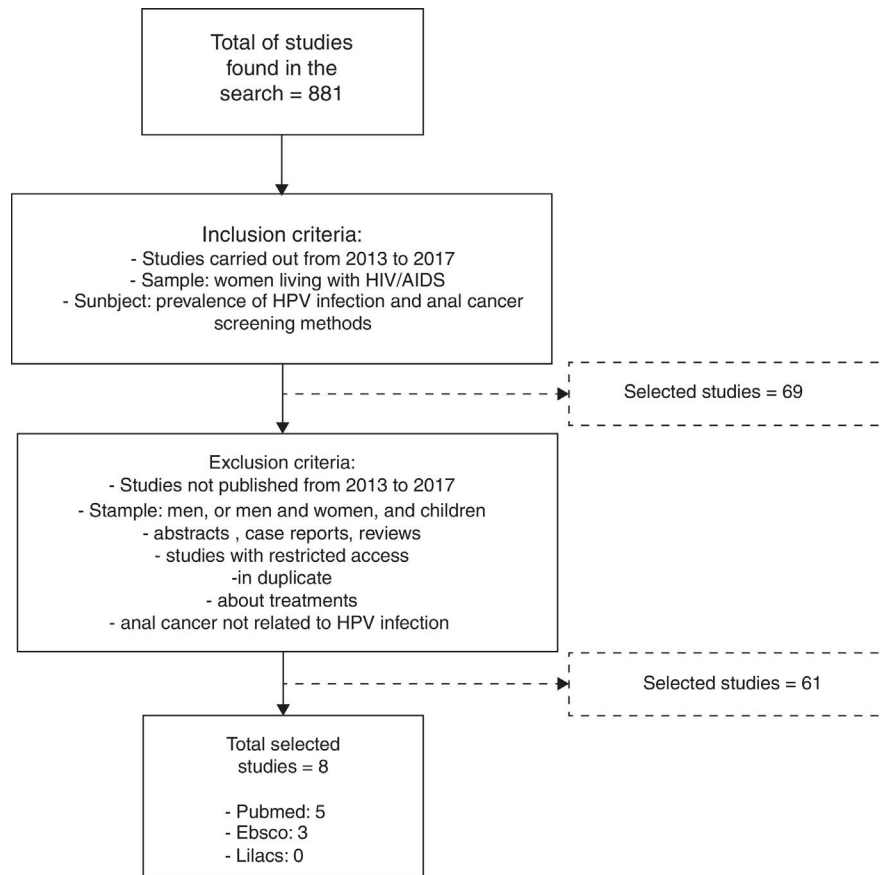
Article	Anal cytology	Anal HPV	Anoscopy/biopsy	Cervical cytology
A1	292 (39%) changes in baseline cytology 111 (15%) changes in follow-up cytology	<sup>a</sup>	208 (71.2%) performed anoscopy 147 (50%) in baseline cytology and 61 (55%) in follow-up cytology 138 (94%) of baseline cytology showed changes in biopsy 44 (72%) of follow-up cytology showed changes in biopsy HSIL: 38 (26%) in baseline cytology and 11 (18%) in follow-up cytology Anal dysplasia of any degree: 100 (68%) in baseline cytology 33 (54%) in follow-up cytology 1 (0.7%) Anal carcinoma	<sup>a</sup>
A2	148 (74.5%) with changes in cytology 32 (16%) ASC-US 97 (49%) LSIL 19 (9.5%) ASC-H/HSIL	High-risk HPV in 43%	148 performed anoscopy 89 (60.1%) performed biopsy: 72 (48%) LSIL 17 (8.5%) HSIL	138 (70%) with changes in cytology 11 (6%) ASC-US 98 (49%) LSIL 29 (15%) HSIL or ASC-H
A3	120 (25%) with changes in cytology 40 (8.5%) ASC 50 (10.6%) LSIL 30 (6.4%) HSIL	163 (42%) infected with anal and cervical HPV	394 (83.8%) subjected to cytology/anoscopy/biopsy <sup>b</sup>	134 (28.5%) with changes in cytology 48 (10.2%) ASC 63 (13.4%) LSIL 23 (4.9%) HSIL
A4	13 (2.2%) with changes in cytology 11 (1.9%) ASC-US 2 (0.3%) HSIL	88.9% presented high-risk HPV (8 out of 9 tested samples)	<sup>a</sup>	<sup>a</sup>
A5 <sup>a</sup>	14 (2.3%) with changes in cytology 3 (0.5%) HSIL 11 (1.8%) LSIL or less	<sup>a</sup>	<sup>a</sup>	116 (19.4%) with changes in cytology 46 (7.6%) HSIL 70 (11.6%) LSIL or lower atypia degree WLHA with abnormal cervical cytology showed 3.8 times higher risk of abnormal anal cytology
A6	3 (7.5%) with changes in cytology 0 (0%) ASC-US 2 (5%) LSIL 1 (2.5%) HSIL	<sup>a</sup>	<sup>a</sup>	10 (25%) with changes in cytology 2 (5%) ASC-US 6 (20%) LSIL 2 (5%) HSIL 29.4% presented concomitant cervical and anal dysplasia
A7	267 (31%) with changes in cytology 124 (14%) ASC-US 97 (11%) LSIL 13 (2%) ASC-H 33 (4%) HSIL or more	51% had at least one high-risk HPV type	<sup>a</sup>	174 (20%) with changes in cytology 72 (8.4%) ASC-US 86 (10.0%) LSIL 2 (0.2%) ASC-H 14 (1.6%) HSIL AGC 5 (0.6%) WLHA with cervical LSIL cervical are more likely to present abnormal anal cytology
A8	44 (29.3%) with changes in cytology ASC-US/LSIL in 28 (18.7%) ASC-H/HSIL 15 (10.0%) Anal carcinoma 1 (0.6%)	99 (57.9%) presented high-risk HPV 81 (47.4%) presented multiple infections 29 (17%) presented HPV 16 infection	169 (98.8%) performed anoscopy and 69 (34.5%) of them performed biopsy 18 (28.1%) LSIL 10 (15.6%) HSIL 1 (1.6%) anal carcinoma	28 (18%) with changes in cytology 26 (15.3%) ASC-US/LSIL 2 (1.1%) ASC-H/HSIL  WLHA with cervical LSIL cervical are more likely to present abnormal anal cytology

ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; WLHA, women living with HIV/AIDS.

<sup>a</sup> The study did not include tests for this methodology.

<sup>b</sup> The results were not separately presented in the article.

Note: In this study, data on sensitivity and specificity of anal cytology were also described, corresponding to 12% and 91.4%, respectively.



**Figure 1 – Study selection results.**

62.5% of the studies, since it is a widely used method that applies simple and low-cost techniques.<sup>15,16</sup> Liquid-based cytology was performed in 25% of the studies; only one study (12.5%) used the two methodologies: the liquid-based cytology was applied to anal specimens and the conventional cytology was used in cervical samples. Liquid-based cytology is applied to increase the sensitivity and specificity of the cytological examination. It has higher cost and requires specific equipment to make the smear; however, it has the following advantages: a single collection, greater cell preservation, reduced unsatisfactory cytologies and, mainly, preservation of protein molecules and nucleic acids for molecular studies aimed at identifying and typing the HPV virus.<sup>15,16</sup>

Although there are conventional and liquid-based cytology techniques, the literature reports that both can be used successfully in routine cervical screening.<sup>12</sup> This can also be attributed to anal screening, as the cytology techniques used are analogous. Most of the studies that performed out HPV-DNA testing opted for the collection of samples in liquid-based due to the method to allow cytological examination and molecular testing from a single sample.<sup>12</sup>

According to the analysis applied to the positivity indices, anal cytology change cases recorded 26.3%, on average; these cases ranged from 2.2% in Thailand<sup>14</sup> to 74.5% in South Africa.<sup>3</sup> This difference may be explained by the health condition and quality of life of the studied population living in the countries where the studies were carried out. According to the “2016

Human Development Report”,<sup>17</sup> issued by the United Nations Development Program, Thailand has better life expectancy at birth (74.6 years) in comparison to South Africa (57.7 years), which also shows higher prevalence of people living with HIV/AIDS (19.2%) than Thailand (1.1%).

The prevalent cytological changes found in the WLHA investigated in the herein reviewed studies were classified as atypical squamous cells of undetermined significance (ASC-US) and as low-grade squamous intraepithelial lesion (LSIL), according to the Bethesda System.<sup>10</sup> Goeieman et al.<sup>3</sup> recorded the highest index of cases showing these two changes 16% and 49%, respectively. The second highest index was recorded by Cambou et al.<sup>5</sup> with 14% (ASC-US) and 11% (LSIL). It is atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H) and high-grade squamous intraepithelial lesion (HSIL) in case of ASCUS, however, most of the studies condensed the results into a single category; therefore, it was not possible knowing the exact numbers recorded for each of these changes. The highest prevalence of ASC-H/HSIL were also recorded in the study by Goeieman et al.<sup>3</sup> with 9.5% positivity, it was followed by Heard et al.,<sup>1</sup> who recorded 10% positivity. Heard et al.<sup>1</sup> also reported the only anal carcinoma case identified through anal cytology.

Anoscopy should be used as follow-up method in case of any anal cytology change. Half of the studies reported that WLHA underwent anoscopy, according to recommendations for anal cancer screening and diagnosis. Goeieman

et al.<sup>3</sup> and Hessel et al.<sup>2</sup> performed anoscopy in all WLHA who showed anal cytology changes, whereas Gaisa et al.<sup>4</sup> performed anoscopy in 71.2% of them. Heard et al.<sup>1</sup> performed anoscopy in 169/171 participants regardless of the cytology result; 69 of these patients underwent biopsy. The number of anal changes found in their study was almost the double in the anoscopy, which was followed by biopsy (45.3%), in comparison to the results recorded in the anal cytology (29.3%).

HPV infections happen due to virus penetration in epithelial microfissure. The virus prefers the region in the transformation zone, where there is transition between the squamous and the glandular epithelium, and where the reserve cells are also located in.<sup>18</sup> The defense system in these cells is not yet developed, fact that facilitates the development of anal neoplasia.<sup>19</sup> Most HPV infections are intraepithelial and asymptomatic. In addition, they are eliminated from the body through the action of the immune system; they may be of subclinical and/or transitory nature.<sup>18,20</sup> Some of them may be latent; however, they may be reactivated and lead to the development of benign clinical lesions such as anogenital warts or intraepithelial lesions. These lesions may regress or persist and develop into anal cancer.<sup>18,19</sup>

HPV infection recorded 56.5% positivity, on average, in the HPV-DNA tests conducted in the selected studies. Heard et al.<sup>1</sup> found 57.9% prevalence of high-risk HPV infection, whereas Pittyanont et al.<sup>14</sup> recorded 88.9%. However, resource-poor countries show limited anoscopy and HPV-DNA test availability.<sup>9</sup> Taylor et al.<sup>21</sup> reported that HPV infection appears to be higher in WLHA than in non-HIV-positive women, mainly the high oncogenic risk types such as HPV 16 and 18. In addition to immunosuppression, WLHA show increased likelihood of developing anal lesion, which may evolve into anal cancer when it is not diagnosed and treated.<sup>6</sup>

The natural history of HPV infection may change in case of HIV coinfection; HPV viral load may remain elevated even in WLHA who adhere to antiretroviral therapy.<sup>22</sup> Brickman and Palefsky<sup>23</sup> performed a meta-analysis on the epidemiology and pathogenesis of HIV/HPV coinfection; they found that low CD4<sup>+</sup> T-cell count over a long period of time is associated with the development of cervical and anal cancer, as well as that it is a characteristic often found at the time these neoplasms are diagnosed.

Six studies also presented cervical cytology results; four of them found that history of cervical lesion is one of the risk factors for the development of anal cancer. According to Bisherwal et al.,<sup>9</sup> 29.4% of the study participants presented concomitant cervical and anal dysplasia. Cambou et al.<sup>5</sup> and Heard et al.<sup>1</sup> found that WLHA with cervical LSIL are also prone to show abnormal anal cytology.

Despite the low sensitivity and high unsatisfactory sample rates found in the anal cytology, WLHA with cervical cytology changes are 3.8 times more likely to present abnormal anal exam.<sup>7</sup> Studies indicate that the anus may be an HPV reservoir, as well as that the risk of developing anal lesion may increase in the presence of undetected and untreated cervical lesions.<sup>8,24</sup> However, according to Kost et al.,<sup>6</sup> regardless of negative results for injury and cervical infection caused by HPV, the anus may present positive HPV infection and consequent risk of developing anal lesion, fact that makes it necessary adopting screening methods. Thus, although

cytology shows limitations, it is a screening method that should be taken into consideration due to the increase in anal cancer cases, mainly in WLHA.<sup>7</sup>

According to the National Cancer Institute (INCA – Instituto Nacional de Câncer),<sup>25</sup> anal tumors are more often diagnosed in women. Thus, the “Clinical Protocol and Therapeutic Guidelines for HIV Infection Management in Adult Individuals”<sup>26</sup> recommends performing annual anal cytology examination in WLHA, according to the immunological standard (CD4<sup>+</sup> T-cell above 200 cells/mm<sup>3</sup>), and twice a year when CD4<sup>+</sup> T cell are below 200 cells/mm<sup>3</sup>.

This neoplasm is not included in the “Brazilian Cancer Incidence Estimate”<sup>27</sup> reports due to its low incidence, fact that hinders the accurate epidemiological knowledge in the country and may be one of the reasons for the lack of planning of anal cancer screening policies. Although these recommendations are in place, studies describing anal screening techniques and their results in the country remain scarce.

Moreover, only one study presented data on the sensitivity and specificity of cytology. These are important information to evaluate the benefits of implementing the method in screening anal cancer. Thus further studies are needed that contemplate this description.

Some limitations were found during the current integrative review. A small number of studies involving only WLHA was found during the article selection stage. Most of them were studies whose sample comprised men and women, or gay men. In addition, during the analysis of the selected studies, it was possible seeing that their methodologies varied, as well as that there was no standardization in the way they described the results.

Nevertheless, the authors of the herein selected studies were unanimous about the concern with high anal cancer and anal HPV infection rates, as well as about the importance of adopting screening procedures to prevent this neoplasm. Some authors reported anal cytology as screening method,<sup>3–5,7,9,14</sup> whereas others argued that, due to its limitations, cytology should be associated with HPV detection methods in order to better estimate the risk of developing (or not) anal cancer in the future.<sup>1,2</sup>

## Conflicts of interest

The authors declare no conflicts of interest.

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