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Clinical Benefit of a Conservative Treatment for High-Risk Human Papillomavirus Lesions in Patients with HIV

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Abstract

Infection with Human immunodeficiency virus (HIV) shows a higher risk of infection by Human papillomavirus (HPV). We aim to provide evidence about the effect of a *Coriolus versicolor*-based vaginal gel (Papilocare®) for treating HPV in women with HIV. Women ≥25 years coinfected by endocervical HPV and with low-grade abnormal cervicovaginal cytology were treated for 6 months with Papilocare® in this observational, prospective, non-controlled pilot study. Cytology, colposcopy, biopsy, hybrid capture test, and 5-point Likert scale were assessed to evaluate cervical lesions repair, HPV clearance, and changes in cervical reepithelization, respectively, at 6 months. Fifteen patients (25–54 years) were included. Overall HPV clearance and cytological normalization rates were 73.3% and 80.0%, respectively, and 55.6% of the abnormal colposcopies were normalized. Re-epithelialization index improved in 66.7% of cases. Papilocare® may be effective for managing endocervical HPV infection in patients living with HIV.

Keywords: Human papillomavirus, Human immunodeficiency virus, cervical lesion, *Coriolus versicolor*-based vaginal gel, HPV persistence

Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection globally and is behind nearly all cases of cervical cancer (CC).[1] While most HPV infections clear spontaneously within a year, a small percentage (10%–15%) persist, significantly increasing the risk of progression to precancerous lesions.[2] Persistent infection with high-risk HPV (HR-HPV) genotypes is the primary driver of CC development, largely due to the oncogenic activity of viral proteins.[3] HR-HPV E6 and E7 oncogenic proteins have pleiotropic functions, inhibit apoptosis, and dysregulate the cell cycle, and their expression is needed for malignant transformation.[3] Expression of E6 and E7 can also impact the immune response by downregulating the expression of toll-like receptors, which are responsible for activating the innate immune response, as well as altering the macrophages' activation by cytokines.[3] T-helper (Th) cells, a subset of T cells (CD4), which belong to the adaptive immune response, might differentiate into two distinct populations, Th1 and Th2. Interestingly, in an HPV lesion, the ratio of Th2 and Th1 is shifted, leading to an increase in Th2 subpopulation and suppression of the cellular response, which is considered the dominant response needed for HPV clearance and regression of HPV-dependent cervical lesions.[3,4]

The inability of the immune system to clear the infection can lead to viral persistence, progression of disease, development of HPV-dependent lesions, and increased rates for the acquisition of other pathogenic infections.[2,5] Related to this, HPV could predispose to infection with the Human immunodeficiency virus (HIV) and its dissemination through the disruption of the epithelium integrity and the mucosal immune system.[6] Different studies have shown that HIV increases the risk of HPV infection,[7] usually exceeding 30%. Thus, patients infected with HIV have a higher risk of HPV incidence, higher viral load, persistence, and progression rates of HPV-dependent cytological alterations.[8,9]

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It has been demonstrated through some studies that women with HIV are six times more at risk of developing CC, and it is estimated that up to 5% of all CC cases can be attributed to HIV-derived immunosuppression, which affects the CD4 cell population, necessary for clearing the virus.[9,10] Some studies have found that women with HIV with a high CD4 count (>500 cells/mm^3) are at greater risk of acquiring HPV compared with women who are HIV-negative. However, as CD4 counts decline, particularly below 200 cells/mm^3, the risk of persistent HPV infection increases substantially, as low CD4 levels impair the immune system's ability to clear the virus effectively.[9] CC rates and its precursor lesions are significantly elevated in women infected with HIV compared with the general population and it has been speculated that these rates might increase further as women with HIV live longer due to the use of anti-retroviral therapy (ART).[11] In addition, it is well known that HPV-related malignancies are expected to decrease due to the efforts of scale-up in vaccination, which has set a target of 194 countries by 2030 through the Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem.[12] However, patients with HIV presented lower seroconversion rates compared with immunocompetent patients.[13]

Cervical lesions are classified depending upon the proportion of the thickness of the epithelium showing mature and differentiated cells: Cervical intraepithelial lesion (CIN 1) (low-grade) involves the lower 1/3 or less of the epithelium, while CIN 2 and 3 (high-grade) progress to include more than a third to the entire epithelium thickness.[14]

Currently, there is no treatment for women who are diagnosed with CIN 1 other than to observe the evolution and treat if the infection becomes persistent and progresses to CIN 2 or 3. Then, patients are treated with an excisional procedure.[15] These invasive treatments have associated risks such as preterm birth.[16] In addition, they may also facilitate the acquisition of infections,[17,18] which represents a risk for patients who are immunosuppressed.

Moreover, HIV and/or HPV has an important impact on the quality of life (QoL) of patients with HIV/HPV, since they present an increased psychosocial burden and comorbidities related to the stigma of being infected,[19–21] the consequences of sexual intercourse, sexual dissatisfaction,[20] and depressive symptoms,[19,22] among others. Also, it has been proved that a positive HPV diagnosis and abnormal cytology are associated with fear and anxiety.[23] The exposure to this psychological stress induces the release of cortisol, which results in the alteration of the immune response by altering the nuclear factor-κB signal transduction pathway, that regulates the expression of inflammatory genes. Cortisol also inhibits the maturation of the vaginal epithelium and the accumulation of glycogen. Consequently, vaginal-free glycogen and *Lactobacillus* levels are reduced, leading to a decrease in lactic acid synthesis.[24,25] Moreover, HPV infection itself has recently been described as an inducer of bacterial dysbiosis, as HPV is able to inhibit the synthesis of an essential peptide for the survival of *Lactobacillus*.[26,27] This creates a dysbiotic environment that leads to the proliferation of anaerobic bacteria associated with bacterial vaginosis such as *Gardnerella* and the acquisition of sexually transmitted infections such as HPV infection. The depletion of *Lactobacillus* spp. and the presence of specific anaerobic taxa are associated with a slower regression of lesions and CIN 2 persistence.[28]

In summary, the immune system is the main responsible for HPV clearance and lesions regressions. Therefore, people with a debilitated immune system like patients living with HIV have a higher risk of lesion progression. Moreover, other factors such as the integrity of the cervical epithelium, the vaginal microbiota, and the psychological stress influence the inflammatory response against the HPV. Furthermore, the clinical approach for HPV infection/CIN 1 confirmation among patients with HIV, focuses on regular and lifelong screening due to their increased risk of CIN 3 starting within 1 year of sexual activity. Excisional treatment is indicated when histological high-grade squamous intraepithelial lesion (HSIL) (CIN 2 or CIN 3) is diagnosed.[6] Hence, there is a need for novel therapies that can promote viral clearance, facilitate regression of CIN 1 lesions, and reduce the substantial disease burden caused by HPV in this particularly vulnerable population.

Recent results from previous clinical studies indicate that a *Coriolus versicolor*-based vaginal gel (Papilocare®) has an effect in repairing HPV-derived cervical lesions, increasing viral clearance rates, and improving the vaginal microbiota state among patients who are immunocompetent.[29–31] Papilocare® vaginal gel combines ingredients known for their properties, such as moisturizing, tissue regeneration, and maintenance of vaginal microbiota balance (hyaluronic acid, *Centella asiatica*, *Aloe vera*, and α-glucan oligosaccharide). Additionally, it incorporates other components with proven positive effects on HPV-dependent cervical lesions and HPV clearance (*Coriolus versicolor*, *Azadirachta indica*, and carboxymethyl-β-glucan). Furthermore, the inclusion of Neem extract (*Azadirachta indica*), as well as *C. versicolor* contributes to inducing a local immune response, as observed in both *in vitro* and *in vivo* model studies, thereby impeding the oncogenic effects of HPV.[29]

However, its potential usefulness among patients with HIV needs to be evaluated. The aim of the present study is to assess the potential effect of the Papilocare® vaginal gel on HPV-dependent low-grade cervical alterations in patients coinfected with HIV.

Materials and Methods

Study design

This was an observational, prospective, descriptive, non-controlled pilot study.

Patients were recruited from the Complejo Hospitalario de Jaén, Spain. Inclusion criteria included: women with HIV and ≥25 years who were also infected by one or more strains of HPV (positive HPV test) in the cervix and with atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesions (LSIL) cytology result.

Women who had no HIV-HPV coinfection or with HPV-dependent high-grade cervical alterations HSIL cytology, major changes in colposcopy and/or CIN 2/3 biopsies, and those who were pregnant or with known allergies to Papilocare® were excluded.

Patients were treated with Papilocare® vaginal gel (Procare Health Iberia, SL. Barcelona, Spain), one cannula/day for 21 consecutive days during the first month. After a 7-day rest period, a single dose cannula was administered every other day for 5 months. The treatment started after the menstrual period and the cannulas were administered at night prior to bedtime. During the treatment, usage of intimate washes and other products that could affect the adhesion of the therapeutic gel to the vaginocervical mucosa was contraindicated but sexual intercourse was not restricted.

The study was performed in accordance with the good practice guidelines for biomedical investigation in the Declaration of Helsinki and with the Spanish Asociación Española de Patología Cervical y Colposcopia (AEPCC) and American American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines for cervical pathology.[32] All patients were required to read the patient information sheet and to sign the informed consent form to participate in the study. The investigation was approved under protocol number 1724-N52 but not monitored by the Clinical Research Ethics Committee of Complejo Hospitalario de Jaén "as it is the clinical evaluation of an approved therapy for cases such as those of the patients included in the study protocol and there are no indications of specific risk to patients with HIV in the summary of product characteristics not in the literature available to date."

Study procedures and measurements

Patients were visited before starting the treatment (baseline visit) and after 6 months of treatment (final visit). In the first visit, data about patients' backgrounds (age, smoking, ART, hormonal therapy) were collected. In both visits, data collected included HPV presence, cytology, colposcopy, and biopsy when necessary. Also, *Gardnerella* and *Chlamydia* vaginal swab, HIV viral load, and lymphocyte count were collected.

The primary endpoint was the repair of the cervical alterations. To evaluate it, cytology, colposcopy, and biopsy (when necessary) were performed at baseline and after 6 months of Papilocare® vaginal gel treatment. The colposcopy findings were classified in accordance with the colposcopy terminology currently accepted by the International Federation of Cervical Pathology and Colposcopy: normal, abnormal [minor changes (grade 1; G1), major changes (grade 2; G2), non-specific], suspicious for invasion and miscellaneous findings.[33–35]

Secondary objectives included the evaluation of HPV clearance, the degree of cervical reepithelization, and the viral load and the lymphocyte (CD4) count to control the potential influence of HIV infection-derived immunological status on the results. These parameters were determined with a maximum difference of 2 weeks from the cervix observations. A hybrid capture test and a 5-point Likert scale were assessed for HPV clearance and degree of cervical reepithelization, respectively. The degree of cervical epithelialization was quantitatively rated with a 5-point Likert scale with scores ranging from 1 to 5, where 5 represents no ectopy, 4 represents mild ectopy (with less than 25% of the outer cervix orifice compromised), 3 represents moderate ectopy with 25%–50% of the outer cervix orifice compromised, 2 represents severe ectopy that affected over half of the cervical orifice, and 1 represents cases of severe ectopy with bleeding. Assays for *Chlamydia* and *Gardnerella* were also part of the secondary objectives.

Tolerability and adherence to the treatment were also assessed by reporting possible adverse effects and direct questioning by the investigator at the follow-up visit, respectively.

All the data collected as part of this study is included in this article.

Results

Baseline characteristics of the patients are described (Table 1). A total of 15 patients with HIV who were

Table 1. Baseline Characteristics of the Studied Patient Series

Case	*Age*	*ART therapy*	*Smoking*	*Hormone therapy*	*Cytology*	*Endocervical HPV genotypes*	*Condylomas*	*Colposcopy (IFCPC 2011)*	*Biopsy*
1	41	No	Yes	No	ASC-US	6, 11, 16, 18	No	Normal	N.P.
2	49	Yes	Yes	No	ASC-US	16, 68	No	Normal	N.P.
3[a]	38	Yes	Yes	No	ASC-US	11, 16, 31	No	G1 abnormal	CIN 1
4[a]	47	Yes	No	No	LSIL	16, 18, 35	No	G1 abnormal	CIN 1
5	53	Yes	Yes	No	ASC-US	6, 16, 18	No	Normal	N.P.
6	50	No	No	No	ASC-US	18, 33	No	Normal	N.P.
7[a]	31	Yes	No	No	LSIL	18, 59	No	G1 abnormal	CIN 1
8[a]	33	Yes	No	No	ASC-US	11, 16	No	G1 abnormal	CIN 1
9[a]	29	Inconsistent	Yes	Yes	LSIL	16, 18, 52	No	G1 abnormal	CIN 1
10[a]	25	Inconsistent	Yes	No	ASC-US	5, 16, 18, 31, 45, 68	Vulvar	G1 abnormal	CIN 1
11	54	Yes	Yes	No	ASC-US	16, 35	No	G1 abnormal	CIN 1
12	44	Yes	No	No	LSIL	16, 18	No	G1 abnormal	CIN 1
13	39	Yes	Yes	No	LSIL	16, 18, 35	No	G1 abnormal	CIN 1
14	35	Yes	Yes	No	ASC-US	16, 68	No	Normal	N.P.
15	49	Yes	Yes	No	LSIL	6, 11, 16	No	Normal	N.P.

[a]Indicates the variables corresponding to cases with AIDS.

ASC-US, atypical squamous cells of undetermined significance; ART, antiretroviral therapy; CIN, cervical intraepithelial neoplasia; G1, grade 1 (minor changes); HIV, human immunodeficiency virus; HPV, human papillomavirus; IFCPC; International Federation for Cervical Pathology and Colposcopy; LSIL, low-grade squamous intraepithelial lesion; N.P., not performed.

coinfected with HPV from 25 to 54 years (mean age was 41.1 years old) were included. One patient was not under ART and two others were inconsistent with it. A total of 67% of patients were smokers and one (6.7%) patient was using hormonal therapy. Six (40%) patients fulfilled the criteria for acquired immune deficiency syndrome (AIDS) showing CD4 count results of less than 200 cells/mm^3.[36] Viral load was not detected (N.D.) in 10 (66%) patients. In six (40%) patients, the cytological changes suggested an LSIL, while the cytological reports for the other nine (60%) patients described ASC-US. No moderate, severe dysplasia or carcinoma (HSIL/CIN 2-3+) cases were found. All the patients (100%) were infected with high-risk HPV (HR-HPV) 16/18 and with at least one other HPV genotype. One (6.7%) patient had vulvar condyloma while the other 14 (93%) presented normal genitalia. All patients who presented normal colposcopy were not referred to biopsy analysis. None of the patients were vaccinated against HPV.

A comparison of baseline and post-treatment (6 months) statuses for each patient in the study is described (Table 2). Regarding the cytological results, 12 (80%) patients showed normalization, whereas 2 (13%) of them persisted, and 1 (6.7%) regressed after 6 months of treatment with Papilocare® vaginal gel. For the colposcopy results, six (40%) patients showed normal colposcopy at baseline and after 6 months of treatment, whereas five (33.3%) patients with G1 lesions at baseline regressed to normality after 6 months of treatment, reaching 73.3% of cytological normalization with concordant colposcopy (lesions repaired) after 6 months of treatment. However, four (27%) patients left persisted in their G1 lesions after 6 months of treatment. Colposcopy-directed biopsy was performed on nine (60%) patients who showed G1 abnormal colposcopy in the baseline visit. All of them were diagnosed with CIN 1. After 6 months of treatment with Papilocare®, only four (26.7%) patients still showed a G1 abnormal colposcopy. The results from the biopsy showed a persistence in CIN 1 for all of them. The other 11 (73.3%) patients showed normal colposcopy and a biopsy was not performed.

The overall viral clearance was achieved by nine (73.3%) patients and partial clearance of the HPV-endocervical colonization was seen in two (13.3%) of them.

The qualitative re-epithelialization rate improved in 10 (66.7%) patients, providing a total average benefit of 0.8 points (from 3.13 to 3.93). Regarding the immunological status, the variations observed in the viral load and the lymphocyte count at baseline and after the 6 months of treatment were not clinically significant (Table 2). No *Chlamydia* and *Gardnerella vaginalis* infections were detected, neither at baseline nor after 6 months of treatment. Most patients (86.7%) showed adherence to the recommended therapy, without any associated severe adverse effects. Only two patients (13.3%) reported mild side effects; one case referred to an "excessive sensation of genital humidity" and another one reported a "self-limiting mild vulvar pruritus during the first 2 weeks of treatment." However, none of them prevented the completion of the recommended treatment regimen.

Discussion

Immunosuppression plays a crucial role during HPV infection, particularly in the early stages, which are infection acquisition, persistence, and any possible progression from low-grade cervical lesions to high-grade cervical lesions.[9] Currently, the low-grade cervical lesions are managed by active surveillance.[18]

Papilocare® vaginal gel has shown efficacy in increasing the regression and HPV clearance rates in patients who are immunocompetent, hence might also be an option for patients who are immunosuppressed such as women with HIV who are coinfected with HPV. The persistence of HPV infection is influenced by viral, host, and environmental factors, including genotype, multiple concurrent infections, viral load, HIV coinfection, age, and smoking. In our cohort, these factors are obvious, as patients present characteristics such as immunosuppression by HIV infection, HR-HPV genotypes, older age, smoking habits, and HIV coinfection.[5,37]

In the present study, we observe a clinical benefit in patients with HIV and coinfected with HPV under treatment with Papilocare® vaginal gel. Although patients with HIV with a persistent HPV infection experience significantly increased rates of precancerous lesions compared with those who have been infected with HPV for less than 6 months,[9] 80% of our patients experienced cytological normalization, similar to 88% of normalization rates in the PALOMA randomized clinical trial (RCT).

HIV modifies HPV pathogenesis,[9,10] increasing the risk of HPV persistence and reactivation. In fact, low CD4$^+$ lymphocyte count (<200 cells/mm^3) is the strongest independent predictor of HPV infection[36] among patients with HIV. Of our 15 patients, 6 (40%) meet AIDS criteria. Of these patients, four (66.7%) persist at CIN 1. Given that three of the persisting patients have CD4$^+$ levels under 200 cells/mm^3 and, furthermore, two patients are non-compliant with Papilocare® treatment, these could be influencing factors contributing to the lack of lesion regression.

In our study, after 6 months of treatment, 73.3% of patients experienced a total viral clearance, albeit being infected with HPV 16 or 18, and/or other HR-HPV, which are implicated in about 70% of CC cases globally.[10] These are remarkable results, as in the PALOMA RCT, the percentage of patients who experienced HPV clearance was lesser, reaching a 63%.[29]

Regarding the age, our cohort's average age was 41.13 years old, which is also favorable for HPV infection progression, as proved in a meta-analysis that states that women over 40 years were at higher risk of HPV persistence and CIN development.[38] Finally, tobacco has been identified as an immune modulator, inhibiting T-cell responses against HPV infections, and interfering with lesion regression.[39] Considering that 66.67% of our patients with immunosuppression were also smokers, the regression of the lesions might become more challenging.

Studies up to date have not been fully conclusive about the impact of ART on HPV-related disease progression, despite adherence to the treatment. Lofgren et al.[40] reported that 38% of the patients positive for LSIL regressed to normal cytology during a 2-year follow-up. In contrast, 66.7% of patients positive for LSIL from our study presented normal cytology after ART treatment during a 6-month follow-up. Further studies should confirm if these higher regression rates are due to Papilocare® vaginal gel treatment.

Table 2. Comparison of Baseline and Post-Treatment (6 Months) Statuses for Each Case from the Series

	Endocervical HPV genotypes		*Cytology*		*Colposcopy (IFCPC 2011)*		*Colposcopy-directed biopsy*		*Cervical epithelialization rate (Likert scale[a])*		*CD4 count (cells/mm^3)*		*Viral load (copies/mL)*	
Cases	*Baseline*	*6 months*	*Baseline*	*6 months*	*Baseline*	*6 months*	*Baseline*	*6 months*	*Baseline*	*6 months*	*Baseline*	*6 months*	*Baseline*	*6 months*
1	6, 11, 16, 18, 68	11, 18	ASC-US	Negative	Normal	Normal	N.P.	N.P.	3	3	1431	201	N.D.	N.D.
2	16	N.P.	ASC-US	Negative	Normal	Normal	N.P.	N.P.	4	5	700	601	N.D.	N.D.
3	11, 31, 16	N.P.	ASC-US	Negative	G1 abnormal	Normal	CIN 1	N.P.	4	5	490	440	N.D.	N.D.
4	16, 18, 35	N.P.	LSIL	Negative	G1 abnormal	Normal	CIN 1	N.P.	3	4	318	497	5,321	4,827
5	6, 16, 18	N.P.	ASC-US	Negative	Normal	Normal	CIN 1	N.P.	4	4	597	600	N.D.	N.D.
6	18, 33	18, 33	ASC-US	Negative	Normal	Normal	CIN 1	N.P.	5	5	615	794	N.D.	N.D.
7	18, 59	N.P.	LSIL	LSIL	G1 abnormal	G1 abnormal	CIN 1	CIN 1	4	4	119	186	36,575	36,800
8	11, 16	N.P.	ASC-US	Negative	G1 abnormal	G1 abnormal	CIN 1	CIN 1 focal	4	5	208	111	1,210	1,348
9[b]	16, 18, 52	N.P.	LSIL	ASC-US	G1 abnormal	G1 abnormal	CIN 1	CIN 1	3	4	324	296	110,000	207,006
10[b]	5, 16, 18, 31, 45, 68	16, 18, 31, 68	ASC-US	ASC-US	G1 abnormal	G1 abnormal	CIN 1	CIN 1	2	4	107	91	420,466	517,200
11	16, 35	N.P.	ASC-US	Negative	G1 abnormal	Normal	CIN 1	N.P.	2	3	625	575	N.D.	N.D.
12	16, 18	16, 18	LSIL	Negative	G1 abnormal	Normal	CIN 1	N.P	3	4	410	506	N.D.	N.D.
13	16, 18, 35	N.P.	LSIL	Negative	G1 abnormal	Normal	CIN 1	N.P.	2	4	327	302	N.D.	N.D.
14	16, 68	N.P.	ASC-US	Negative	Normal	Normal	N.P.	N.P.	3	3	521	412	N.D.	N.D.
15	6, 11, 16	N.P.	LSIL	Negative	Normal	Normal	N.P.	N.P.	1	2	470	303	N.D.	N.D.

N.D., non-detectable.
[a]Likert scale, scores ranging from 1 to 5, where 5, no ectopy; 4, mild ectopy; 3, moderate ectopy; 2, severe ectopy; and 1, severe ectopy with bleeding.
[b]The patient reported not having followed treatment with Papilocare®.

As the HPV clearance and normalization rates observed in this study are similar to those observed in the population with immunosuppression, it might be possible that the coadjuvant treatment with Papilocare® vaginal gel has contributed to this observation. Nonetheless, more studies with larger cohorts of patients with and without ART and stratified by immunocompetence level are needed to confirm this efficacy. Thus, it has been recently suggested that the proportion of $CD4^+$ leukocytes versus the total number of leukocytes might be a more accurate way of measuring the immunocompetence state.[41] In this regard, new studies should include this data.

Despite this challenging population, Papilocare® vaginal gel offers the opportunity to target other factors that have also been identified as being involved in viral persistence,[23,42–44] thereby promoting viral clearance and regression of lesions.[29]

In a previous study, Papilocare® vaginal gel has proved a 43% of qualitative epithelization improvement.[45] It has been established that cervical ectopy may increase susceptibility to HPV infection[46,47] as it is vulnerable to physical trauma and facilitates HPV infection and replication.[47–49] In the present study, 66.7% of the patients improved the qualitative re-epithelialization rate, which could be one of the driving factors of HPV clearance rates higher than expected for this population.

Lastly, the adverse events experienced by our cohort of patients are similar to the ones reported in previous studies.[27] Only two patients experienced mild side effects which did not prevent them from the completion of the treatment. These results point out that the safety and tolerability of Papilocare® vaginal gel in a population with immunosuppression might be similar to the general population, although wider studies are needed to confirm this point.

To summarize, Papilocare® vaginal gel might represent a useful clinical tool for patients with HIV having low-grade cervical lesions, increasing lesion regression and HPV clearance rates when it is used as a coadjuvant treatment during the active surveillance period. To our knowledge, this is the first study reporting the use of a new conservative therapy against HPV infection among patients living with HIV.

Some limitations must be pointed out: it is a descriptive study, with a small sample size, limited follow-up, and the population only presented infection by HPV or mild associated damage. This hinders the comparative analyses against other published data. Additionally, it would be desirable to have a comparative Papilocare®-non-treated group, as well as a stratified comparison based on the immunological state. Despite our limitations, our study showed encouraging results as the use of Papilocare® vaginal gel could be an effective therapy in the management of endocervical HPV infection in patients with HIV by increasing HPV clearance and cervical normalization rates, obtaining similar effects as in patients without immunosuppression.

Conclusions

The treatment of HPV-dependent LSIL with Papilocare® vaginal gel could be a safe and effective tool in patients who are also positive for HIV. These promising results obtained from a small cohort of patients, with especially poor prognosis due to their smoking habits, age above 40, and HIV infection are in agreement with data previously reported in studies with patients with HPV who are immunocompetent.[29,31,50] Nevertheless, further clinical studies are needed to confirm these findings.

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Author's Contributions

Conceptualization: J.J.H.E., A.L.C.G., A.C.F.R., J.C.P.L. Data curation: J.J.H.E., A.L.C.G., A.C.F.R., J.C.P.L. Formal analysis: J.J.H.E., A.L.C.G., A.C.F.R., J.C.P.L. Funding acquisition: J.J.H.E. Investigation: J.J.H.E., A.L.C.G., A.C.F.R, J.C.P.L. Methodology: J.J.H.E., A.L.C.G., A.C.F.R., J.C.P.L. Project administration: J.J.H.E. Resources: J.J.H.E. Software: J.J.H.E. Supervision: J.J.H.E. Validation: J.J.H.E. Visualization: J.J.H.E. Roles/writing—original draft: J.J.H.E., A.L.C.G., A.C.F.R., J.C.P.L., G.F.R. Writing—reviewing and editing: J.J.H.E., A.L.C.G., A.C.F.R., J.C.P.L., G.F.R.

Author Disclosure Statement

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