






High rates of anal Merkel Cell Polyomavirus and HPV co-infection among people living with HIV

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Abstract

Knowledge of Human Polyomavirus (HPyV) infection in the anal area and its association with sexually transmitted infections such as Human Papillomavirus (HPV) and Human Immunodeficiency Virus (HIV) remains limited. Therefore, anal specimens from 150 individuals of both sexes were analyzed for screening purposes. HPV DNA was found in 50.7% of cases, with a predominance of high-risk (HR) genotypes. HPyV DNA was found in 39.3% of samples, with Merkel Cell Polyomavirus (MCPyV) being the most common, with a higher viral load than JCPyV and BKPyV. In addition, MCPyV viral load increased in people living with HIV (PLWH) with HPV infection ($p < 0.0001$).

KEYWORDS

HIV, HPV, HPyV

Sara Passerini and Matteo Fracella contributed equally to this manuscript.

Carolina Scagnolari and Valeria Pietropaolo share the leadership.

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1 | INTRODUCTION

Sexually transmitted infections (STIs) pose a significant risk of morbidity and mortality worldwide and are associated with a burden of both benign and malignant diseases, primarily affecting the anogenital tract.¹ In recent decades, anal cancer has attracted interest because its incidence has increased significantly in developed countries, in both women and men, and even more so in specific risk groups such as men who have sex with men (MSM), people living with Human Immunodeficiency Virus (HIV) (PLWH) and organ transplant recipients.² In this context, viral persistence is a crucial prerequisite for high-risk (HR) Human Papillomavirus (HPV)-associated tumor growth, such as anal squamous cell carcinoma. PLWH are more likely to be coinfecting with HPV.³ Remarkably, HIV can alter epithelial integrity, thereby favoring not only HPV but also other opportunistic infections, including Human Polyomaviruses (HPyVs). Following an initial asymptomatic infection at young age, HPyVs establish lifelong persistence with low levels of replication and shedding. However, in immunocompromised conditions, viral reactivation can occur, posing a significant pathogenic threat.⁴ Of note, HPyVs, including JCPyV, BKPyV and Merkel Cell Polyomavirus (MCPyV), have been associated with various human disease and the detection of HPyVs DNA in semen suggest their possible transmission through sexual contact.^{4,5} However, our understanding of HPyVs infection in the anal area, and its potential role in HPV-driven malignancies remains limited. Hence, we aimed to investigate the prevalence of MCPyV, JCPyV and BKPyV in the anal district of both women and men, with a particular focus on their incidence alongside HPV and HIV co-infections.

2 | MATERIALS AND METHODS

This retrospective study was conducted on stored anal specimens from 150 individuals attending the proctological clinic and the Department of Infectious Diseases of the Policlinico Umberto I, Sapienza University Hospital in Rome, from January 2017 to December 2021. Participants were referred to the clinic by a general physician, either because of symptoms related to anal HPV infection or for screening purposes. All PLWH were on antiretroviral therapy (ART) and virologically suppressed. The local ethics committee approved the study protocol (Hospital "Policlinico Umberto I", Sapienza University of Rome). All study participants gave written informed, and patients' data were anonymized.

Anal specimens were collected using an anal brush, centrifuged at low speed, and processed for DNA extraction using the QIAamp Blood & Tissue Kit (Qiagen, Hilden, Germany), according to the manufacturer's protocol. From the purified DNA, the human leukocyte antigen (HLA) region was targeted to assess the efficacy of the nucleic acid extraction, while a 450 bp fragment from the L1 HPV region was amplified using the consensus primers MY09 and MY11, as previously described.⁶ HPV genotypes were identified by Sanger sequencing (Bio-Fab research) and stratified according to the IARC

classification into HR HPV group 1 (carcinogenic to humans), HR HPV group 2 A/2B (probably carcinogenic to humans), and low-risk (LR) HPV or group 3 (unclassified as carcinogenic to humans).⁷ In addition, MCPyV, JCPyV and BKPyV DNA was measured by quantitative PCR (qPCR) assays targeting the small T antigen (sTAg),⁸ Large T Antigen (LTAg) and Viral Protein 1 (VP1) regions,⁹ respectively (Supporting Information S1: Table S1). Viral loads, expressed as genome equivalents/milliliter (gEq)/mL, were determined using standard curves from 10-fold plasmid dilutions, with a detection limit of 10 DNA copies/reaction. Samples positive for HPyV DNA were subjected to PCR for amplification of the NCCR and VP1 regions, followed by Sanger sequencing (Supporting Information S1: Table S2).^{9,10} Sequences were compared with reference strains deposited in GenBank (BKPyV strain: AB211371; JCPyV strain: AB081613; MCPyV strain: MCC350/EU375803) and aligned using the ClustalW2 program. Analysis of JCPyV and BKPyV VP1 gene typing regions was based on single nucleotide polymorphisms (SNPs) for classification of JCPyV and BKPyV genotypes/subtypes.^{9,10}

The Shapiro-Wilk test was used to test whether the data followed a normal distribution. Logistic regression tests were performed to assess associations between age, sex, presence of anal lesions, HPV infection, HPV IARC risk classification, HIV infection, MCPyV infection/viral load, JCPyV infection/viral load, BKPyV infection/viral load and co-infections among the viruses tested. For categorical variables, Fisher's exact test (FE) was used to assess statistical differences between independent groups. To identify possible risk factors for the development of HPV, HIV, MCPyV, JCPyV and BKPyV infections, odds ratios (OR) were calculated using sex as the exposure parameter. The Kruskal-Wallis test with Dunn's multiple comparison test (KW) was used to assess differences in MCPyV, JCPyV and BKPyV viral loads between patients with single infections, co-infections with HPV and co-infections with HPV and HIV. $p < 0.05$ were considered statistically significant. Statistical analysis was performed using JASP (version 0.18.10) and GraphPad Prism (version 10.0.0).

3 | RESULTS

Anal specimens were collected from a total of 150 enrolled individuals, including 58 women [mean age 49.9 years, standard deviation (SD) 15.4] and 92 men (mean age 47.4 years, SD 12.7). Most of them ($n = 111/150$; 74%) had no anal lesions, whereas 39 of 150 (26%) had anal low-grade squamous intraepithelial lesion. Demographic and virological characteristics of the study participants are shown in Table 1.

HIV status was known in 130/150 cases, with 32.3% (42/130) identified as PLWH. Of the HPV-positive cases ($n = 76/150$; 50.7%), 2/76 could not be typed due to mixed infections; of the samples with an identified HPV genotype, 27/74 (36.5%) were carcinogenic HR HPV of IARC group 1, 14/74 (18.9%) were of groups 2A or 2B, and 33/74 (44.6%) were LR HPV, including HPV120 ($n = 1/33$; 3%), which is a cutaneous genotype of the Beta genus. The most commonly

TABLE 1 Demographic and virological characteristics of study participants.

Items	Total patients (n = 150)	HPyV-positive (n = 59/150)		p value*
		MCPyV- positive (n = 49/59) ^a	BKPyV-positive (n = 3/59) ^a	
Gender				
Male, N (%)	92/150 (61.3)	32/92 (34.8)	1/92 (1.1)	<0.001
Female, N (%)	58/150 (38.7)	17/58 (29.3)	2/58 (3.4)	<0.001
Age in years, mean (SD)	48.4 (14)	47.2 (14)	60 (10.8)	0.081°
HPyVs viral load (gEq/mL), median (95% CI)		4.3×10^5 ($3.2 \times 10^5 - 4.8 \times 10^5$)	3.1×10^2 ($2.2 \times 10^2 - 4.8 \times 10^2$)	<0.001°
Canonical HPyVs NCCR, ^b N (%)		49/49 (100)	0/3 (0)	
Archetype HPyVs NCCR, ^b N (%)		0/49 (0)	3/3 (100)	
Nucleotide changes (F ₂₁₇ G → A), ^b N (%)		NA	NA	
Nucleotide changes (P ₁₉ A → G), ^b N (%)		NA	1/3 (33.3)	
Co-Infections				
HPV positive, ^c N (%)	76/150 (50.7)	28/76 (36.8)	1/76 (1.3)	<0.001
HR HPV (Group 1) positive, ^c N (%)	27/74 (36.5)	14/27 (51.8)	0/27 (0)	<0.001
HR HPV (Group 2A/2B) positive, ^c N (%)	14/74 (18.9)	5/14 (35.7)	0/14 (0)	0.012
LR HPV (Group 3) positive, ^c N (%)	33/74 (44.6)	9/33 (27.3)	1/33 (3)	0.009
PLWH, ^d N (%)	42/130 (32.3)	13/42 (31)	1/42 (2.4)	<0.001
HPV positive among PLWH, ^d N (%)	32/42 (76.2)	12/32 (37.5)	1/32 (3.1)	<0.001

Note: Data are expressed as number (frequency) or mean (standard deviation, SD)/median (95% CI). Statistical analysis was performed using Fisher's exact test (*) to compare categorical variables and Kruskal-Wallis test (°) to compare continuous variables between MCPyV-positive, JCPyV-positive and BKPyV-positive patients.

^aFour patients tested positive for both MCPyV and JCPyV; one patient tested positive for both MCPyV and BKPyV.

^bSequence analysis of MCPyV, JCPyV and BKPyV NCCR.

^cn = 2/76 HPV infections could not be typed due to mixed infections. HPV genotypes were stratified according to the IARC classification into HR-HPV group 1, also known as human carcinogens (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59), HR-HPV group 2A/2B, or possible and probable carcinogens (HPV68 and HPV26, 53, 66, 67, 70, 73, 82, 30, 34, 69, 85 and 97), and LR HPVs or group 3 not classified as carcinogenic to humans (HPV 6, 11, 28, 32, 40, 42, 43, 44, 54, 55, 57, 61, 62, 71, 72, 74, 81, 83, 84, 86, 87 and 89), including the detected cutaneous genotype of Beta genus (HPV120).

^dData on HIV status were available for 130/150 patients.

detected genotypes were HPV58 ($n = 11/74$; 14.9%), HPV6 ($n = 9/74$; 12.2%), HPV16 ($n = 7/74$; 9.5%), HPV11 ($n = 5/74$; 6.8%) and HPV18 ($n = 4/74$; 5.4%).

Concerning HPyVs distribution among patients, 59/150 (39.3%) were positive for at least one HPyV. Notably, MCPyV DNA was found in 49/150 (32.6%), JCPyV DNA in 12/150 (8%) and BKPyV DNA in 3/150 (2%) of samples tested. MCPyV was identified as the most common HPyV infection in both women (29.3%) and men (34.8%) ($p < 0.001$, FE test). Higher rates of MCPyV viral load were observed in participants compared to JCPyV and BKPyV ($p < 0.0001$, KW test; Table 1). Notably, differences were found between MCPyV and JCPyV median viral loads (4.3×10^5 gEq/mL versus [vs.] 7.5×10^2 gEq/mL; $z = 5.156$; $p < 0.0001$) and between MCPyV and BKPyV median viral loads (4.3×10^5 gEq/mL vs. 3.1×10^2 gEq/mL; $z = 3.281$; $p = 0.003$).

When examining the co-infection patterns of HPyVs, the most common combination was MCPyV and JCPyV, identified in 4/150 samples, while only one patient tested positive for both MCPyV and BKPyV. A canonical NCCR structure identical to the reference sequence of the North American prototype MCC350, strain EU375803, was observed in all MCPyV-positive samples. All JCPyV- and BKPyV-positive samples showed an archetypal sequence with some point mutations. Specifically, the G to A transition at nucleotide position 217 in box F, within the nuclear transcription factor-1 (NF-1) binding site, was observed in 3/12 (25%) of JCPyV-positive samples. Regarding the BKPyV NCCR sequence, an A to G transition at nucleotide position 19 in box P was detected in 1/3 (33.3%) of samples (Table 1). HPyV-positive samples were further analyzed for the VP1 region. Notably, MCPyV VP1 sequencing revealed some nucleotide differences in 15/49 (30.6%) samples that did not result in amino acid changes in the derived protein sequence. JCPyV VP1 sequence analysis identified the European genotype 1A in 9/12 samples, while the European genotype 1B was found in 3/12 samples. A prevalence of subtype I/subgroup b-2 was observed in BKPyV positive samples ($n = 3/3$).

Among HPV-positive patients ($n = 76$), MCPyV infection was the most common ($n = 28/76$; 36.8%), followed by JCPyV ($n = 5/76$; 6.6%) and BKPyV ($n = 1/76$; 1.3%) infections ($p < 0.001$; FE test). Notably, co-infection rates of carcinogenic HR-HPV (group 1) with MCPyV were significantly higher than those with JCPyV and BKPyV (51.8% vs. 7.4% vs. 0%, respectively; $p < 0.001$, FE test). Furthermore, among PLWH with HPV infection, 12/32 also tested positive for MCPyV, 1/32 for BKPyV and none for JCPyV (37.5% vs. 3.1% vs. 0%; $p < 0.001$; FE test; Table 1). None of the analyzed data followed a normal distribution (Shapiro-Wilk test). To identify potential risk factors for HPV, HIV and HPyV infection and/or co-infection, ORs were calculated using sex as the exposure parameter, suggesting that men are more likely to have anal HPV infection (OR: 8.7 [95% CI: 4–19; $p < 0.001$]). No statistically significant correlation between MCPyV viral load and the presence of anal squamous intraepithelial lesions was found. Furthermore, an increased MCPyV viral load was observed in MCPyV/HPV/HIV coinfecting patients compared to those coinfecting with MCPyV/

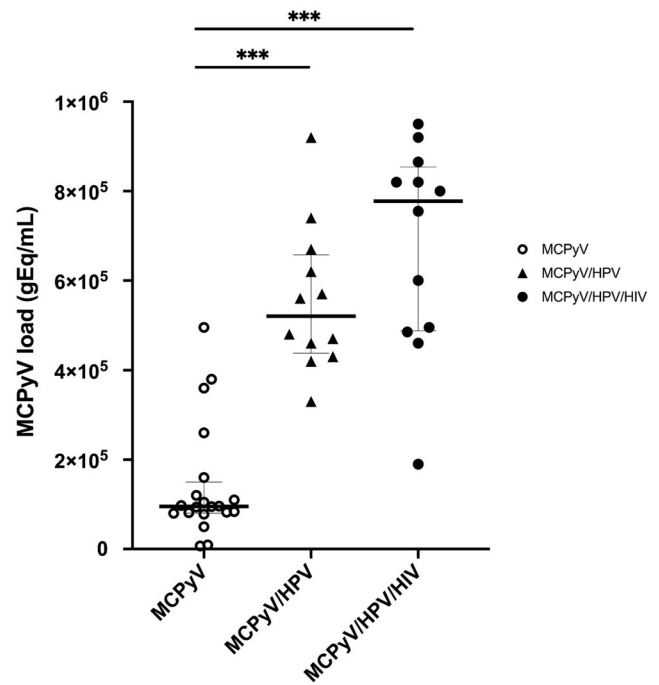


FIGURE 1 MCPyV viral loads in anal brushings. MCPyV viral loads, expressed as gEq/mL, were measured in anal cells from MCPyV-positive-only patients ($n = 20$), MCPyV/HPV coinfecting patients ($n = 12$) and MCPyV/HPV/HIV coinfecting patients ($n = 12$). Data are expressed as mean HPyV titers from three independent experiments, each performed in duplicate. Statistical analysis was performed using the Kruskal-Wallis test with Dunn's multiple comparison test ($*p < 0.05$; $**p < 0.01$; $***p < 0.001$).

HPV only and those positive for MCPyV only ($p < 0.0001$; KW test). Notably, differences were observed between MCPyV infection ($n = 20$) and MCPyV/HPV co-infection ($n = 12$) (9.7×10^4 vs. 5.2×10^5 [median values]; $z = 3.578$; $p < 0.001$) and between MCPyV infection ($n = 20$) and MCPyV/HPV/HIV co-infection ($n = 12$) (9.7×10^4 vs. 7.8×10^5 [median values]; $z = 4.724$; $p < 0.001$) (Figure 1). Comparisons for JCPyV and BKPyV viral loads could not be performed due to lack of data.

4 | DISCUSSION

The role of HPyVs as STIs is largely speculative, as patients generally remain asymptomatic or present with nonspecific anogenital symptoms. Studies investigating anal HPyVs infection in MSM reported HPyV DNA in anal swabs and MCPyV as the most frequently detected, approximately in 30% of the analyzed specimens.^{11,12} MCPyV DNA was also found in 30% and 26% normal anal mucosal samples and anal intraepithelial neoplasia samples, respectively.¹³ However, there is still limited data on the presence of MCPyV, JCPyV and BKPyV in the anal region of both women and men. Therefore, the aim of the present study was to investigate the prevalence of anal HPyV infection and its association with HPV and HIV in a cohort of 150 participants of both sexes.

The cumulative prevalence of anal HPV infection among the enrolled patients was remarkably high, reaching 50.7%; HR HPVs (both IARC Group 1 and Group 2A/2B) accounted for 55.4% of the genotypes identified, highlighting the oncogenic potential of HPV in the anal area. Notably, the oncogenic HPV58, HPV16, and HPV18 genotypes were the most frequently detected, consistent with previous studies.^{6,14} High frequencies of LR HPV genotypes 6 (12.2%) and 11 (6.8%) were also observed. Although not classified as carcinogenic in humans, HPV6 and HPV11 have been detected in cancer cells and have been associated with anal malignancies.¹⁵ Gender has also been identified as a significant risk factor for anal HPV infection, with men at higher risk than women. In addition, a high rate of HPV positivity was observed in PLWH (76.2%), confirming the increased susceptibility of this specific risk group to anal HPV infection.³

Similarly to previous studies, among HPyVs, MCPyV infection was the most common, found in 32.6% of samples tested, followed by JCPyV (8%) and BKPyV (2%). MCPyV had a similar prevalence in both the female (29.3%) and male (34.8%) anal regions, as observed in the respiratory tract.¹⁶ In addition, MCPyV infection was significantly associated with HPV positivity (36.8%), especially with carcinogenic HR HPV genotypes (51.8%). We suppose that our results could be partially explained by previous *in vitro* experiments suggesting that MCPyV could potentially act as a co-factor in up-regulating the expression of HPV oncoproteins, with implications for HPV-induced cancers.¹⁷ Consistently with what observed by Peng and colleagues, the MCPyV positivity rate was particularly high in PLWH (31%)¹¹ and even higher in PLWH with HPV infection (37.5%), confirming that immunosuppression can enhance an actively replicating virus whose infection persists throughout life. Therefore, the high recovery of MCPyV DNA in anal specimens may represent a persistent and asymptomatic infection of the anal region by a pathogen that may be sexually transmitted, as remarked also by MCPyV findings in anal swabs of MSM.¹² Since it is well recognized that HPyVs NCCR is a hypervariable region whose rearrangements may influence replication efficiency and virulence properties, thus being associated with HPyV-caused disease such as nephropathy for BKPyV and progressive multifocal leukoencephalopathy (PML) for JCPyV,^{4,9} in this study, we examined the NCCR sequence of HPyV-positive samples. Typically, NCCR mutations and rearranged variants are observed during host immunodeficiency resulting from genetic defects, viral infections or immunomodulatory treatments.^{9,18} However, the specific mechanism by which the immune system may contribute to viral persistence or reactivation remains poorly understood. Contrary to NCCR analysis conducted on rectal swabs from HIV-1 positive individuals, which reported transitions, transversions and deletions,¹⁹ all 49 MCPyV-positive samples revealed a canonical NCCR. Since the role of NCCR mutations in MCPyV infection remains elusive, further investigations are needed to explain the discrepancy between these findings and to better understand the impact of NCCR strains in MCPyV pathogenesis. An archetypal structure was observed for the JCPyV and BKPyV NCCR, suggesting rare rearrangements in this anatomical region. The JCPyV and BKPyV NCCR alignments showed only single point

mutations that did not affect viral replication. In general, the archetype form is persistent, and the rearranged form arises during or after reactivation,²⁰ suggesting that HPyVs establish persistent anal infections. In addition, molecular analysis of MCPyV, JCPyV, and BKPyV VP1 sequences showed highly conserved regions with noncoding nucleotide variations. Moreover, JCPyV genotype 1 was found to be predominant, whereas the prevalence of subtype I was reported for BKPyV. However, as only a few samples tested positive for JCPyV and BKPyV, further studies are needed to make assumptions about their genomic variability in the anal tract. Also, the absence of patients with high-grade squamous intraepithelial lesions (HSIL)/anal cancer and the lack of quantitative HPV load analysis are limitations of the study that prevent a comprehensive assessment of the relationship between anal clinical manifestations and MCPyV/HPV/HIV co-infections, as well as MCPyV viral load, and highlight the need for further research. More specifically, concerning HPyVs, it would be interesting to compare BKPyV, JCPyV and MCPyV levels in normal tissue, low- and high-grade squamous intraepithelial lesions to assess whether MCPyV may play a role in anal disease.

In conclusion, this study provides, for the first time to our knowledge, valuable insights into the epidemiology of anal HPyV infection, particularly MCPyV, in the context of HPV and HIV co-infection. Given the increased occurrence of MCPyV in anal swabs, coupled with the recognized oncogenic properties of MCPyV, there is an urgent need for further investigation into the potential sexual transmission and plausible role of HPyV in the development of anal canal disease in high-risk populations such as PLWH.

AUTHOR CONTRIBUTIONS

Sara Passerini: Conceptualization; investigation; data curation; writing—original draft preparation; writing—review and editing. **Matteo Fracella:** Conceptualization; investigation; data curation; writing—original draft preparation; writing—review and editing. **Domenico Benvenuto:** investigation; data curation; writing—original draft preparation. **Ginevra Bugani:** resources; investigation. **Alessandra D'Auria:** investigation. **Eleonora Coratti:** investigation. **Giulia Babini:** investigation. **Ugo Moens:** writing—review and editing. **Eugenio Nelson Cavallari:** resources. **Carlo Torti:** writing—review and editing. **Guido Antonelli:** writing—review and editing. **Massimo Ciccozzi:** writing—review and editing. **Alessandra Pierangeli:** writing—review and editing; funding acquisition. **Gabriella d'Ettore:** resources; writing—review and editing. **Carolina Scagnolari:** Conceptualization; data curation; writing—original draft preparation; writing—review and editing; supervision; funding acquisition. **Valeria Pietropaolo:** Conceptualization; data curation; writing—original draft preparation; writing—review and editing; supervision; funding acquisition. All authors reviewed the results and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no commercial or financial conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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