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Prevalence of HPV in anal cancer: exploring the role of infection and inflammation

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Abstract

Anal cancer incidence is rising globally, driven primarily by human papillomavirus (HPV) infection. HPV, especially high-risk types 16 and 18, is considered a necessary cause of anal squamous cell carcinoma. Certain populations like people living with HIV, men who have sex with men, inflammatory bowel disease patients, smokers, and those with compromised immunity face elevated risk. Chronic inflammation facilitates viral persistence, cell transformation, and immune evasion through pathways involving the PD-1/PD-L1 axis. HIV coinfection further increases risk by impairing immune surveillance and epithelial integrity while promoting HPV oncogene expression. Understanding these inflammatory processes, including roles of CD8+T cells and PD-1/PD-L1, could guide development of immunotherapies against anal cancer. This review summarizes current knowledge on inflammation's role in anal cancer pathogenesis and the interplay between HPV, HIV, and host immune factors.

Keywords HPV, Anal cancer, Inflammation, PD-L1, IBD, HIV

Introduction

The global incidence of anal cancer has been steadily increasing. Data from studies indicate that between 2001 and 2015, the annual incidence rate of anal cancer rose by 2.7%, accompanied by a 3.1% annual increase in mortality [1]. Though uncommon in the general population, anal cancer is on the rise in certain populations, particularly those living with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), men who have sex with men (MSM), women who have cervical cancer, vaginal precancer and cancer, smokers, and those whose immune systems have been compromised by organ transplants, steroids, or other immune-suppressive medications [2–4]. Since there has been a noticeable increase in incidence of anal cancer globally over the past few decades, it has become more important to understand the pathophysiology and risk factors for the disease [5]. Figure 1 has summarized the relative risk factors for anal cancer. Less than 5% of cancers of the gastrointestinal system are anal cancers. Given that the presenting symptoms of anal canal cancer often resemble those of benign anorectal illnesses, diagnosis can be challenging [6]. Anal squamous cell carcinoma (ASCC) is typically referred to as "anal cancer" [7].

HPV infection is thought to be a required cause of ASCC, which is expected to affect 29,000 people annually, most of whom are women [7]. Moreover, HPV plays a significant role in the prevalence of anal cancer, with

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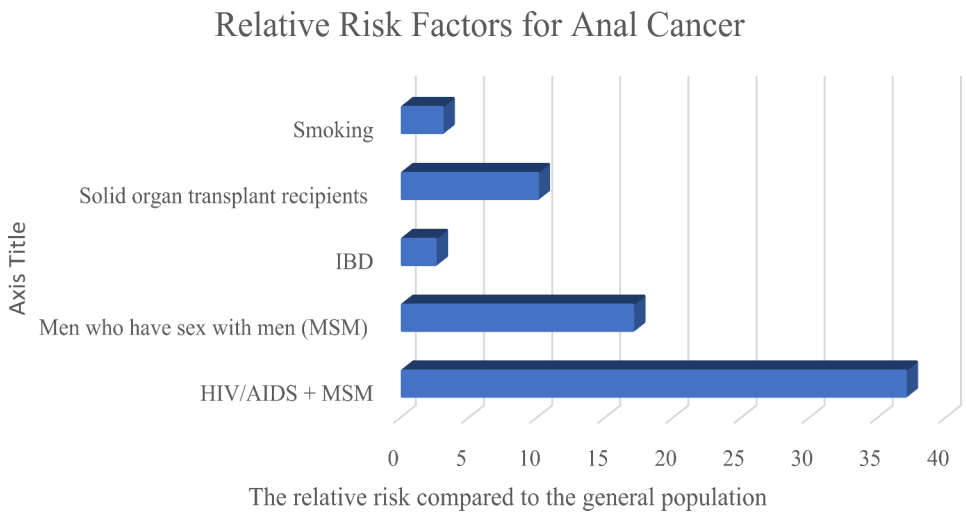

Fig. 1 The risk factors for anal cancer

approximately 88% of anal cancer cases testing positive for HPV DNA, making it one of the cancers most strongly associated with HPV after cervical cancer. The prevalence of HPV in anal intraepithelial neoplasia (AIN) grades 2 and 3 is even higher, around 94% [8]. Among the various HPV types, HPV16 is the most frequently detected, accounting for a substantial proportion of cases followed by HPV18 in the next place [8]. Preventive measures like vaccination are crucial to reducing future incidences of this disease [9]. There has also been a notable increase in the incidence of anal cancer in developed countries, with rates rising by about 2% annually since the 1970s [10]. Furthermore, in one study conducted in Scandinavia, 73% of anal cancer specimens had HPV DNA matching type 16, and 84% of specimens had HPV DNA matching either or both of the other types [11].

Tumorigenesis is known to be significantly influenced by a complicated inflammatory response to infection. We provide an overview of the literature's current resources on the association between inflammation and the development of anal cancer in this review.

The diagram highlights that HIV/AIDS in HIV-positive MSM carries the highest relative risk of 37-fold increase for anal cancer. This is followed by being a solid organ transplant recipient (10-fold increased risk), being MSM without specifying HIV status (17-fold increased risk), having inflammatory bowel disease (2-3-fold increased risk), and smoking (2-4-fold increased risk).

HPV infection, prevalence, mortality

HPVs are small, non-enveloped, double-stranded DNA viruses that are members of the papillomaviridae family [12, 13]. Based on differences in their genetic sequence, over 200 different typeshave been found [14]. Mucosal HPV types have been divided into two categories: low-risk HPVs (LR-HPV), which are not carcinogenic, and high-risk HPVs (HR-HPV), which are types with recognized oncogenic potential [15]. HR-HPV types include HPV16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. Of these, two HPV types (16 and 18) account for a significant percentage of anogenital and oropharyngeal cancers as well as more than 70% of cervical malignancies. The HPV types 6, 11, 42, 43, and 44 are classified as LR-HPVs. Of these, LR-HPV types 6 and 11 are accountable for over 90% of benign genital warts [15–17]. Cervical cancer is caused by persistent HPV infection with high-risk HPV types, which is also linked to malignancies of the vulva (69%), vagina (75%), mouth/throat (70%), penis (63%), and anal (91%) [16]. HPV infection may contribute to the development of prostate cancer as well [18]. Most HPV infections are rapidly cleared by the host's immune system in a matter of years. But other HPV types lead to chronic infections and ultimately result in a variety of genital and oropharyngeal malignancies [19]. One of the most prevalent sexually transmissible infection (STI), the HPV affects millions of people each year globally. Over 90% of men and 80% of women who engage in sexual activity will at some point in their lives become infected with HPV [20]. In the world in 2019, HPV-related new cases of cancer in women and men were estimated to be 620,000 and 70,000, respectively. In women globally, it ranks as the fourth most prevalent cause of cancer-related fatalities [21]. Roughly 70% of the world's load is distributed among less developed regions [22]. As of right now, vaccination appears to be the most effective way to prevent HPV infection and its associated illnesses. Three vaccines are now on the market and several more are in advanced stages of clinical trials as a result of several studies conducted to lower the burden of virus-related illness. Cervarix (HPV types 16, 18), Gardasil (HPV types 6, 11, 16, 18), and Gardasil9 (HPV types 6,

11, 16, 18, 31, 33, 45, 52, 58) are these vaccinations [23, 24].

Anal cancer, prevalence

The global incidence of anal cancer is rising. Anal cancer is one of the cancers with a recognized HPV etiology, with approximately 90% of cases being HPV-driven [25]. There is interest in determining HPV infection's possible function in the pathogenesis of other malignancies due to its proven significance in the etiology of cervical cancer [5]. As a result, it is now generally acknowledged to play a significant role in the carcinogenesis of epithelial squamous cell carcinomas in a variety of sites, including the anogenital tract and oropharynx [26]. With 27,000 new cases reported globally in 2008 and age-adjusted incidence rates of roughly 1 per 100,000 people, anal carcinomas are a very uncommon cancer [27, 28]. Nonetheless, current data suggests that incidence is rising in many nations, and this rise is related to a number of causes, including modifications in sexual behavior [29, 30]. One of the most important contributing elements to the carcinogenesis of anal squamous cell carcinoma (SCC) is acknowledged to be HPV infection. By integrating into the host DNA or remaining as extra-chromosomal epitopes, HPV causes normal squamous anal epithelium to undergo a neoplastic transformation that leads to low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL) and ultimately squamous cell carcinoma of the anus (SCCA) [31]. E6 and E7 are two oncoproteins encoded by the HPV genome, whose expression is crucial for the virus's ability to promote cellular proliferation and evade apoptosis in infected cells [32, 33]. E6 causes p53 fragmentation, E7 inhibits Rb, and both E6 and E7 encourage the reactivation of Telomerase reverse transcriptase (hTERT), which results in the immortalization of cancer cells and the growth and dissemination of neoplasms [31, 34]. A recent comprehensive study found that 72% of anal cancer patients had positive HPV DNA tests [26]. Furthermore, a number of studies have shown that 80–97% of people with anal cancer who have been diagnosed also have HPV infection [36–37]. Among HPV types, anal infection is linked to types 6, 11, 16, and 18 [38]. In addition to these types, researchers found a link between anal cancer and types 31, 33, and 45 [39]. The highest risk of developing cancer and AIN are associated with types 16 and 18 [40]. With 73% of all HPV-positive tumors, HPV16 is the most often found type. About 5% of patients had HPV18, which is the second most prevalent type discovered [41]. The risk of developing AIN is increased by a persistent HPV infection with an elevated viral load [42]. Additionally, most precancerous anal lesions (AIN) (91.5% in AIN1 and 93.9% in AIN2/3) have HPV DNA within them [41]. Men who have sexual relations with other men, especially those who are HIV-positive, are at a higher risk of developing anal cancer [43]. HIV-positive women are also more likely to have invasive anal cancer, HSIL and HSIL [44].

Details on anal cancer Some parts of the world lack the distribution of HPV types, with the majority of published findings being from the USA and Europe [45]. It is crucial that sexually transmitted illness education and HPV vaccination campaigns are included into routine clinical practice for both boys and girls [46]. The nine-valent vaccination contains the HPV types linked to anal cancer. Therefore, the 9-valent HPV vaccination should successfully prevent anal cancer when given to boys and girls before they begin sexual engagement [47].

Inflammation and anal cancer

An inherent characteristic of cancer that aids in its growth and spread is inflammation [48]. Chronic inflammation, often resulting from infections, autoimmune diseases, and inflammatory conditions, is recognized as a significant factor in tumorigenesis, facilitating cellular transformation and evasion of immune surveillance [48]. The association between chronic inflammation and cancer development has been well-established, with approximately 20% of cancers linked to chronic infection [5]. Based on the observation that leukocytes are present in neoplastic tissue, Rudolf Virchow formulated the first theory on the correlation between inflammation and cancer [48]. Following then, a great deal of research has been done on the function of inflammation in the development of tumors. Still, its precise significance is not quite clear [49]. Tumor cells are able to evade apoptosis and immune surveillance due to many pathophysiological processes linked to chronic inflammation. These mechanisms result in cellular transformation and multiple alterations in the immune response [50]. HPV infection is a critical risk factor for anal SCC, with studies indicating that 72% of anal cancer patients test positive for HPV [51]. Furthermore, HIV infection significantly increases the risk of anal cancer, with HIV-infected individuals facing a 15 to 40-fold higher risk compared to the general population [51, 52]. The interplay between HPV and HIV coinfection complicates the pathogenesis of anal cancer, as HIV can enhance HPV's oncogenic potential by impairing immune responses and epithelial integrity [53]. Understanding these mechanisms is key to developing more effective prevention strategies and treatment options for anal cancer.

The importance of quick infection diagnosis and prevention is highlighted by these results. Reducing the risks of cancer linked to inflammation may be possible by ongoing education and the deployment of screening programs that prevent the development of chronic infections and inflammations [5]. Current screening programs

like cytology and HPV detection offer important tools for at-risk populations, although their sensitivity and specificity could be enhanced. Promising developments in biomarker tests and the use of high-resolution anoscopy (HRA) as a gold standard for detecting anal precancerous lesions highlight the potential for more effective national screening strategies for anal cancer [54].

In anal cancer, the chronic inflammatory environment created by HPV and HIV infection facilitates the evasion of apoptosis and immune recognition, allowing tumor cells to proliferate and metastasize. Several pro-inflammatory pathways are involved in this process, notably the NF-κB signaling pathway [55]. NF-kB plays a central role in regulating inflammatory responses and has been implicated in various cancers. The classical NF-kB activation pathway is triggered by microbial and viral infections or exposure to pro-inflammatory cytokines like TNF-α and IL-1β [55]. These inflammatory mediators activate the IKK complex, leading to phosphorylation and degradation of IkB proteins. This releases NF-kB dimers to translocate to the nucleus and induce transcription of pro-inflammatory, anti-apoptotic, and cell proliferation genes [55]. Moreover, NF-kB is activated by inflammatory mediators like TNF-α, IL-1β, and induces pro-inflammatory, anti-apoptotic gene expression - Promotes cell survival and proliferation. Constitutive NF-kB activation has been observed in many cancers and is thought to promote oncogenesis by suppressing apoptosis and enhancing cell growth and angiogenesis. However, the role of NF-kB is complex, as it can also promote apoptosis in certain contexts [55].

The role of PD-1/PD-L1 in anal cancer

In the context of prolonged antigen exposure, the checkpoint receptor known as programmed cell death protein-1 (PD-1) is expressed on the surface of different immune cells, including B lymphocytes, macrophages, monocytes, dendritic cells (DCs), myeloid cells, natural killer (NK) cells and tumor-specific activated T cells [56–58]. Tumor cells are the primary source of expression for PD- ligand 1 (PD-L1), the natural PD-1 receptor [59]. Numerous studies conducted in the last few years have validated the clinical relevance of PD-1/PD-L1 antibodies and their influence on human cancer prognosis [60, 61]. Although there are imperfections in the link between this biomarker and its clinical importance, and it differs depending on the type of human cancer [62]. PD-1 suppresses T cell activation during immune responses to avoid autoimmune damage to tissue [63]. Long-term antigen exposure in tumors or persistent infections causes continuous PD-1 expression, which can restrict the immune system's ability to remove pathogens or malignant cells [64]. Research has demonstrated the involvement of PD-1/PD-L1 in the pathophysiology of anal cancer [37]. Viral antigen is constantly present when a persistent viral infection is ongoing. Consequently, over the duration of infection, antigen-specific T lymphocytes are continuously activated. T cell exhaustion is the result, which leads antigen-specific T cells to re ach this condition [65–67]. The effector activities of exhausted T lymphocytes are lost, including a decrease in proliferative and cytotoxic potential as well as a decrease in IL-2 and other cytokine output [68, 69]. It was additionally found that HPV infection and the PD-1/PD-L1 are related. The PD-1/PD-L1 is activated by the oncoproteins E6 and E7 [36]. The local immunological response is therefore suppressed [70]. Extensive research has suggested that the immune response to HPV E6 and E7 oncoproteins may be linked to elevated PD-L1 expression in anal cancer [31]. Tumor-infiltrating lymphocytes (TILs) emit large quantities of IFN-γ, which may upregulate PD-L1 and result in the development of "adaptive immune resistance." [71]. However, it has been demonstrated that there is no correlation between PD-L1 expression and HPV infection. This means that PDL-1 is likely an independent prognostic marker in SCCA, linked to a higher survival rate, as no discernible differences in HPV infection status were found in tumors expressing PD-L1 compared to those PDL1 negative [72]. PDL1 may also serve as a prognostic biomarker for SCCA, which has led to the implementation of treatment approaches that target the PD-1/PD-L1 axis in both non-metastatic and metastatic SCCA [73]. Regarding the relationship between the PD-1/PD-L1 and anal SCC in HPV-positive individuals, there is, still, contradiction [74]. According to some research, increased PD-L1 expression is linked to the development of precancerous lesions and decrease in survival probability in the event of anal SCC [72, 75]. Conversely, it has been noted that PD-L1 expression is connected to better outcomes [37]. According to studies, an inflammatory lymphocytic infiltration that expresses CD8 and PD-1 is present in anal dysplastic lesions; this infiltrate is more common in high-grade lesions. These findings demonstrate how the PD-1/PD-L1 pathway plays a role in the anal dysplasia's natural course [76]. Furthermore, research has demonstrated that HPV has a direct function in the epithelium, triggering the PD-1/PD-L1 pathway and so inhibiting the anticancer activity of cytotoxic cells [76]. These results bolster the usage of imiquimod for anal dysplasia as well [77]. High levels of interleukins, such as tumor necrosis factor alpha (TNF-α) and interferon-alpha (IFN-α), are induced by imiquimod, which activates the innate immune system and may also activate NK and cytotoxic T cells [78]. According to the study of *Govindarajan* et al. 56% of anal cancer samples tested positive for PD-L1, and positive lesions had a worse prognosis (higher rates of local recurrence and death), which supports the idea that anti-PD-1/PD-L1 therapy would be useful [75]. To

fully understand the function of CD8+cell infiltration of tumors and how it relates to PD-1/PD-L1, more investigation is required. These results may prove useful in the application and advancement of immunotherapy for the treatment of anal SCC. It may be possible to increase the cytotoxic activity of CD8+cells by using PD-1 inhibiting drugs. Numerous clinical trials are now being conducted to examine the function of monoclonal antibodies that obstruct PD-1 receptors in anal SCC [37]. According to newly available data, anti-PD1/PD-L1 medication may have encouraging anticancer action in a subset of patients whose anal cancer has already received treatment, providing fresh opportunities for treatment [31].

The role of CD8+ T cell in anal cancer

Recent studies have underscored the critical role of CD8+T cells in ASCC. Hu et al. found that a high density of intratumoral and peritumoral CD8+T cells were associated with favorable clinicopathological characteristics and improved prognosis in patients with ASCC [79]. Specifically, increased CD8+T cell density was linked to better tumor differentiation, earlier-stage diagnosis, and enhanced disease-free and overall survival rates [79]. Moreover, in HIV-infected patients, high intratumoral CD8+T cell density also correlated with improved disease-free survival. These findings highlight the pivotal role CD8+T cells play in the anti-tumor immune response in ASCC [79]. Therapies targeting the PD-1/PD-L1 axis, which can suppress CD8+T cell function, may therefore offer a promising approach for developing immunotherapies in this disease.

Another research by Balermpas et al., underscoring the critical role of CD8+T cells in the context of ASCC, particularly concerning their prognostic significance in patients undergoing chemoradiotherapy, found that high expression of CD8+tumor-infiltrating lymphocytes (TILs) was significantly associated with improved local control and disease-free survival in ASCC patients, particularly those with high HPV16 viral load [80]. Specifically, high CD8+TIL expression correlated with favorable clinicopathological characteristics, including early N stage and increased PD-1+TILs, suggesting a robust immune response against the tumor [80]. The study also demonstrated that elevated levels of PD-1 and PD-L1 were linked to better clinical outcomes, indicating that these immune checkpoints may be pivotal in modulating the anti-tumor immune response. Importantly, the findings advocate for the integration of immune checkpoint inhibitors targeting PD-1/PD-L1 in treatment strategies for ASCC, especially for patients with high HPV16 loads and strong immune cell infiltration, thus providing a rationale for further exploration of immunotherapy in this patient population [80].

Major Histocompatibility Complex I (MHC-I) and the T-cell receptor (TCR) are two mechanisms by which CD8+T-cells recognize antigens and release perforin and granzyme B from their granules, giving them cytotoxic potential [81]. Therefore, CD8+cells can play an important role in the immune response to HPV infection [82]. On the other hand, HIV infection alters CD8+cells' normal function, resulting in decreased efficacy and activity [83]. Defective clearance of viruses and the development of HPV-associated precancerous lesions and anal malignancy were the outcomes of these alterations [84]. Additional research has demonstrated that higher levels of CD8+cell tumor infiltration are linked to better treatment outcomes and a higher rate of survival, which corroborates this finding [79, 85].

Inflammatory bowel disease and anal cancer

Gastrointestinal tract inflammation, whether chronic or recurrent, is linked to inflammatory bowel diseases (IBD) [86]. IBD are characterized by an immunological reaction in the body. Crohn's disease (CD) and ulcerative colitis (UC) are the two most frequent types [87]. As opposed to CD, which affects the intestinal wall, UC affects the upper layer of the large intestine [88]. The incidence of CD and UC can be ascribed to several variables, such as geographic location, genetics, incorrect nutrition, and inadequate immunological response [89]. Weight loss, diarrhea, stomach discomfort, and rectal bleeding are a few of the symptoms of CD and UC. Inflammation is the primary cause of several symptoms, including weight loss, diarrhea, stomach discomfort, and rectal bleeding [90]. The mouth, the anus, and all of the intestinal layers are impacted by CD. UC affects the colon's mucosal layer. Both the gut and the rectum have lesions. The symptoms range from minor to severe and might be fatal [91]. Anal cancer is more common in patients with IBD [92]. Results of a study were published in the Journal of Crohn's and Colitis, and they showed that people with UC and CD had greater risks of anal cancer than the general population [96]. The study reviewed multiple studies on UC and CD to determine the incidence rates of anal cancer. It found that anal cancer is more common in UC patients compared to CD patients. However, among CD patients, those with perianal CD have a higher incidence of anal cancer. The study also noted that there is limited and varied data on the prevalence of anal cytological abnormalities and high-risk HPV in these patients, with no clear link to the use of immunosuppressive drugs [93]. Due to inflammation in the rectum and/or anus as a component of their illness, patients with UC and perianal CD differ significantly from other high-risk groups for anal cancer [94]. The epidemiological study found that patients with CD have a higher risk of developing anal cancer, particularly fistula-associated anal carcinoma,

which arises from perianal fistulas [95, 96]. Anal cancer in CD, hitherto considered to be uncommon, is receiving more and more attention as a result of an increase in published findings [97–102]. However, the dearth of population-based research makes it challenging to pinpoint its precise occurrence [94]. *Beaugerie* et al. conducted a large case–control research in which they prospectively monitored over 2900 patients with a history of anal/perianal CD. The study found that the incidence of adenocarcinoma (ADC) and squamous cell carcinoma (SCC) was 0.38 and 0.26 per 1000 patients/year, respectively [103]. Furthermore, several investigations have established that the primary risk factor for the initiation of anal cancers in CD appears to be a history of perianal fistulas lasting longer than ten years [104–106]. Fistula-associated anal cancer in Crohn's disease likely follows a pathogenesis similar to chronic colitis, beginning with mucosal hyperplasia and persistent inflammation, which subsequently progresses to dysplasia and carcinoma [94, 101]. Additional research is required to elucidate these facets.

HPV and HIV coinfection in anal cancer

The risk of malignancies linked to the HPV rises with immunosuppression [107–109]. Individuals with advanced HIV illness, or AIDS, are more likely to develop invasive and in situ HPV-associated malignancies, such as anal cancer [109]. This increased risk is in line with the high prevalence and long-term nature of anal HPV infection in HIV-positive people [110]. MSMs are at an especially increased risk for anal cancer, regardless of HIV status; however, HIV-positive MSM face an estimated 37-fold higher risk compared to the general population [111–114]. About one in 240 of the 30- to 34-year-olds in this group were predicted to get anal cancer within ten years after receiving an AIDS diagnosis. Furthermore, one in 80 of the same people who were cancer-free after ten years are predicted to get anal cancer during the next ten [115]. Men with HIV (particularly MSM) account for a significant portion of those diagnosed with anal cancer in the US due to their elevated risk of the disease [116, 117]. Anal cancer risk is higher in individuals with HIV infection when their CD4 level is low and immunosuppression appears to be the most significant factor in the early phases of anal cancer development [118, 119]. There is strong evidence that the genesis of anal cancer is linked to immunosuppression associated with HIV [120]. Anal HPV infection has a lower rate of clearance and a longer persistence when HIV is present [121]. According to a research by *Colón-López* et al.,anal cancer incidence was nearly four times greater in AIDS patients than in those with less advanced illness (HIV alone) [122]. Furthermore, a recent analysis from the HIV/AIDS Cancer Match Study, which integrates data from population-based HIV and cancer registries, identified anal cancer as the third most prevalent malignancy with elevated incidence in the HIV-infected population. Among these cases, 83% occurred in HIV-positive MSM, and 71% were in individuals who had been living with AIDS for five or more years [123]. *Wei* et al., in a pooled analysis of 29,900 men, found a higher prevalence of anal HPV in HIV-positive men across all age groups, with nearly half of HIV-positive MSM aged 15–18 infected with high-risk HPV. HIV was linked to increased risk of HSIL and greater HPV persistence, particularly in those with low CD4 counts, aligning with Colón-López's findings [124]. Anal cancer incidence rose with the length of time persons with HIV had low CD4 counts and inadequately controlled HIV infection, according to a large French cohort research [125]. An additional immunosuppressed population, recipients of solid organ transplants, have a much higher risk of anal cancer [126, 127]. It is still unclear exactly what complicated immunological and cellular alterations result from co-infection with HIV and HPV. It was once believed that HIV infection increases HPV's capacity to cause cancer by suppressing the immune system. Nonetheless, current research indicates that modifications to the anal epithelium's microenvironment may result in an elevated carcinogenic potential [128]. Low circulating CD4+cell counts are thought to be only one explanation of the elevated risk, as greater incidence of anal cancer has been reported in HIV-positive persons even in the presence of normal CD4+cell counts [122]. This finding suggests that additional pathways are probably implicated in the cause of anal cancer linked to co-infection with HIV and HPV. As a result, new research has looked into the function of CD8+cells and the PD-1/PD-L1 axis [37]. The latest research indicates that coinfection happens in the anal epithelium locoregionally. HIV damages epithelial integrity, which makes HPV infection easier [53]. Through the CCR5, CXCR4, and CD4 receptors, HIV penetrates cells [129]. The distal portion of the gastrointestinal system is particularly rich in immune cells that have these receptors [130]. Anal epithelial cells are thereby contacted by HIV infection and contaminated immune cells locally [37]. One important component of the pathophysiological pathways is the HIV Tat protein. The HIV Tat protein, which is secreted by HIV-positive immune cells, is thought to infiltrate anal epithelial cells and facilitate the transcription and replication of viral DNA [131, 132]. By upregulating the production of proteins E6, E7, and E2, the HIV Tat protein promotes the replication of the viral genome [37, 133, 134]. Eventually, the use of drugs and other modifiable behavioral variables like condoms should be included in HPV prevention programs.

Table 1 summarizes the key pathways (PD-1/PD-L1, NF-κB), roles of immune cells (CD8+T cells, Tregs), HIV-specific mechanisms (Tat protein, disruption of

Table 1 The key pathways and mechanisms in inflammation-driven anal cancer pathogenesis

Pathway/ Mechanism	Description	Reference(s)
PD-1/PD-L1 Axis	-Suppresses anti-tumor immunity by inhibiting T cell function -Upregulated by HPV E6/E7 oncoproteins and IFN-γ from TILs -Promotes "adaptive immune resistance"	[63] [71] [71]
NF-κB Pathway	-Activated by inflammatory mediators like TNF-α, IL-1β -Induces pro-inflammatory, anti-apoptotic gene expression -Promotes cell survival and proliferation	[55]
Role of CD8 + T Cells	-Recognize and kill HPV-infected/transformed cells -High tumor infiltration associated with better prognosis	[81] [79, 85]
Role of Regulatory T Cells (Tregs)	-Suppress anti-tumor immunity -Increased in HPV-associated cancers like anal cancer	[50]
HIV Tat Protein	-Promotes HPV E6/E7 oncogene expression in anal epithelium -Facilitates HPV genome replication and transformation	[37, 133, 134] [132, 133]
HIV Disruption of Epithelial Integrity	-HIV infection compromises anal epithelial barrier -Facilitates HPV access to basal epithelial cells	[53]
Progression of Lesions	-Normal → AIN 1 → AIN 2/3 → Invasive Anal Cancer	[31]

epithelial integrity), and progression stages involved in inflammation-driven anal cancer development.

Conclusion

In conclusion, the rising global incidence of anal cancer highlights the importance of elucidating the complex inflammatory pathways that drive HPV-induced carcinogenesis in this disease. While HPV infection is a necessary cause, chronic inflammation and immunosuppression, such as from HIV coinfection, facilitate viral persistence and cancer development by disrupting immune control. The PD-1/PD-L1 pathway appears to play a central role in suppressing anti-tumor immunity. A deeper understanding of how HIV, HPV, and inflammation coordinately disrupt CD8 + T cell responses and promote oncogene expression could reveal new therapeutic targets. Immunotherapies blocking the PD-1/PD-L1 axis show promise, but further research is needed on optimizing these approaches based on each patient's viral, inflammatory and immune status. Ultimately, a multifaceted strategy targeting both HPV and the inflammatory tumor microenvironment may be required to improve outcomes for anal cancer patients, especially in high-risk populations.

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Data availability
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Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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