



Skin cancer in patients who are co-infected with HIV/ HBV or HIV/HCV: a systematic review

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Abstract

Skin cancer, the most common cancer in the United States, has been well-described in the literature to be associated with environmental factors including ultraviolet (UV) radiation. However, the effect of chronic viral infections on risk of skin cancer development, particularly in individuals co-infected with Human Immunodeficiency Virus (HIV) and Hepatitis B or C Viruses (HBV/HCV), has yet to be elucidated. This systematic review aims to be one of the first to consolidate existing literature and examine the relationship between skin cancer and HIV/HBV and HIV/HCV co-infections. We conducted a systematic review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, searching MEDLINE, Embase, Cochrane CENTRAL, and Web of Science databases for studies published from inception to March 26, 2024. Inclusion criteria for studies included only those reporting on HBV and/or HCV in people living with HIV (PLWH). Five studies were ultimately included for analysis. The review identified multiple non-melanoma skin cancers (NMSC) and cutaneous adnexal carcinomas in HIV/HCV or HIV/HBV co-infected patients. Notably, Pilomatrixal carcinomas were observed in co-infected individuals. Sarcomas including Kaposi sarcoma and low-grade fibroblastic sarcoma were also linked to HIV/HCV or HIV/HBV infections. However, the studies primarily focused on specific types of cancers without elucidating the underlying mechanisms for the association between HIV/HCV/HBV infection and sarcoma development. In summary, this review suggests a potential link between HIV/HCV and HIV/HBV co-infection and certain types of skin cancer, namely adnexal carcinomas. Further research is crucial to determine the underlying mechanisms, explore the association with different skin cancer types, and identify effective prevention and treatment strategies for co-infected individuals.

Keywords Hepatitis B · Hepatitis C · HIV · Co-infection · Skin cancer

Introduction

Skin cancer is the most common cancer in the United States with an incidence of 5.4 million new cases reported annually just in the United States [1]. While environmental factors, particularly ultraviolet (UV) radiation, are well-established risk factors, the role of chronic viral infections is less well-known [1, 2]. Human Immunodeficiency Virus (HIV) infection weakens the body's immune system, making individuals more susceptible to various cancers, including skin malignancies [3]. Individuals with HIV are also more likely to be co-infected with Hepatitis B virus (HBV) and Hepatitis C virus (HCV) due to shared transmission routes [4]. Worldwide, HBV and HCV are the two most common coinfections with human HIV and are major comorbidities affecting those with HIV [5]. HBV and HCV are mainly

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known to cause chronic liver inflammation and increase the risk of liver cancer (hepatocellular carcinoma) [4].

Patients with HIV/HCV co-infection have faster rates of fibrosis progression resulting in more frequent occurrences of cirrhosis, end-stage liver disease, and hepatocellular carcinoma [4, 6]. The presence of HIV changes the course of HCV infection. Among HIV patients, HCV infection tends to become chronic in over 90% of cases due to the deficiency in critical CD4 T cell responses against HCV [7]. Once chronic HCV infection sets in, fibrosis progresses at a much faster rate, leading to a higher incidence of cirrhosis and its associated complications compared to those with HCV alone [8].

HIV/HBV coinfection also exacerbates morbidity and mortality beyond that caused by either infection alone [9]. Individuals coinfecting with HIV exhibit elevated hepatitis B viremia levels resulting in a fivefold faster progression to chronic hepatitis B compared to those infected solely with HBV [10]. They also have an increased risk of cirrhosis and hepatocellular carcinoma [11]. HIV-related immunosuppression can lead to the loss of hepatitis B surface antibodies and reactivation to chronic hepatitis B [10]. Furthermore, patients with HIV, particularly those with compromised immune systems, show diminished antibody responses to HBV vaccination compared to those without [11]. Managing hepatitis B in patients with HIV is further complicated by the dual activity of certain nucleoside analogs, the emergence of resistant strains of HIV or HBV, limitations of and reduced response to interferons, and the more rapid development of lamivudine-resistant HBV [11].

This co-infection scenario raises concerns not only about liver health but also about the development of extrahepatic malignancies, such as skin cancer. A recent study has shown that HIV/HCV coinfection is associated with a 3.7-fold higher risk of non-liver-related cancers [6]. Furthermore, there have been more studies examining the effects of HCV and HBV on non-liver-related illnesses, including cardiovascular disease, chronic kidney disease, and even mental health [12, 13]. With HIV further weakening the immune system, research indicates that HIV/HCV and HIV/HBV co-infection can worsen these diseases [7, 9]. However, despite extensive research on the link between HIV and liver cancer in co-infected individuals, the specific impact of co-infection with HCV and/or HBV on non-liver cancers, particularly skin cancer, remains poorly understood. This includes the effects of various combinations of co-infections, such as HIV with HBV (HIV/HBV), HIV with HCV (HIV/HCV), and HIV with both HBV and HCV (HIV/HBV/HCV).

To address this gap, this systematic review aims to consolidate existing literature and shed light on skin cancer in patients who are co-infected with HIV/HBV or HIV/HCV.

Method

The systematic review was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. A comprehensive search strategy was developed to locate studies reporting on HBV and/or HCV in people living with HIV (PLWH).

Literature search strategy

We searched MEDLINE, Embase, Cochrane CENTRAL (all via Ovid), and Web of Science, and included all years from each database's inception until the date of the search on March 26, 2024. The search strategy incorporated a combination of database-specific subject headings and keywords representing the concepts of HIV, hepatitis, and skin conditions (see S1 Appendix for full reproducible search strategies). Inclusion criteria included studies on HBV and/or HCV in people living with HIV (PLWH).

Study selection

Three reviewers independently assessed eligibility based on titles, keywords, and abstracts. Any disagreements were resolved through consensus. Articles that met the eligibility criteria were included for the full articles review, which was initially assessed by one reviewer and then verified by the two other reviewers. Reasons for exclusions were documented at each stage and consensus on study selection was reached by discussion. Meta-analysis was not performed within this review.

Results

The systematic literature search yielded 132 results in MEDLINE, 259 results in Embase, 27 results in Cochrane CENTRAL, and 134 results in Web of Science, resulting in 552 articles in total. After removing duplicate records of 150 articles, 402 articles were reviewed for title, keywords, and abstract screening. Among those, 16 full-text articles were assessed for eligibility and 5 articles were included for analysis as shown in Fig. 1. The results of the included studies were described in a narrative synthesis and presented individually for each publication in the results tables (Table 1). The included studies were published between 2008 and 2023. Studies took place in the United States ($n=2$, 40%), following France ($n=2$, 40%), and Tshwane ($n=1$, 20%).

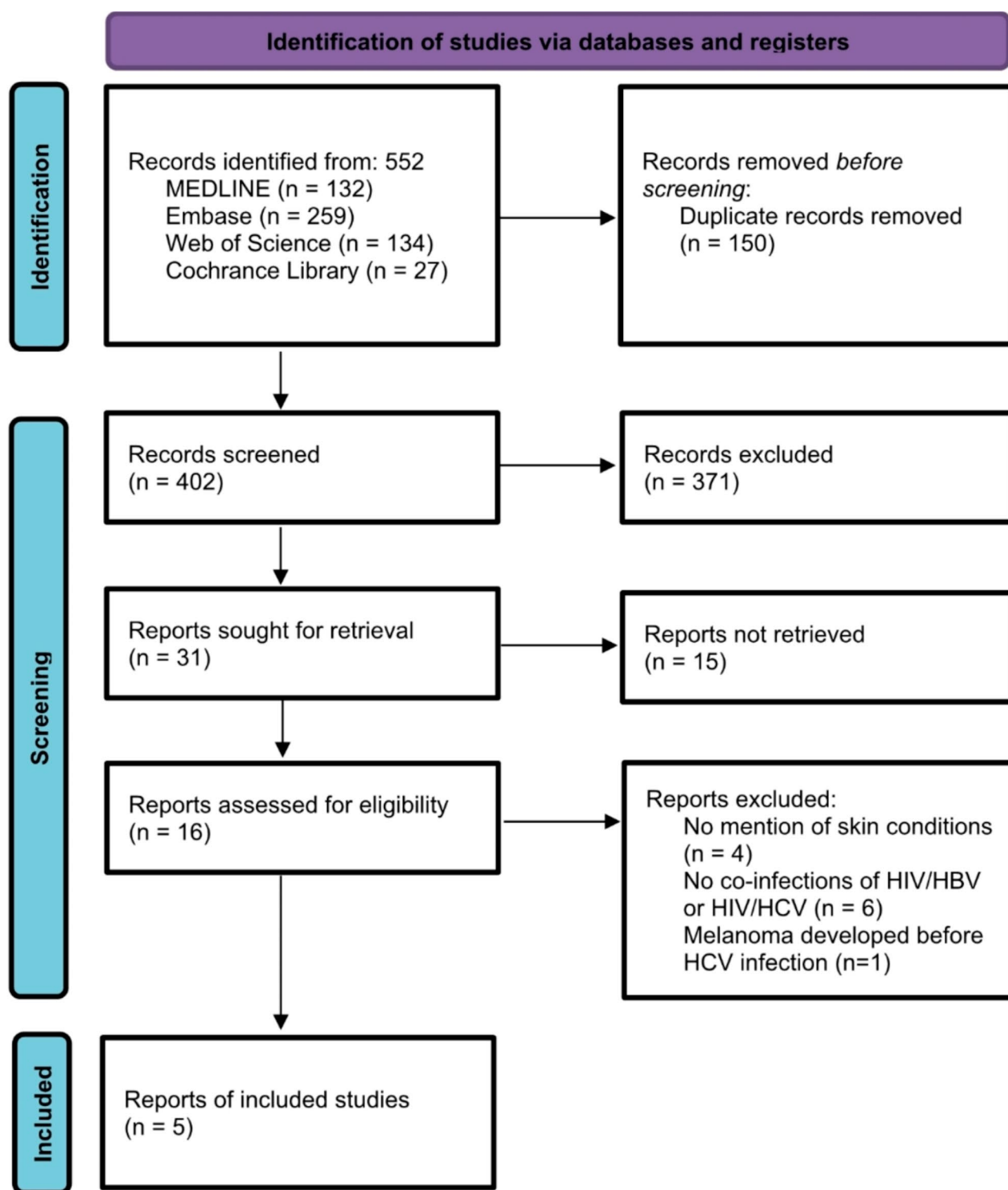


Fig. 1 Flow sheet of the article selection process

Non-melanoma skin cancer (NMSC)

Non-melanoma skin cancer is the most commonly diagnosed form of skin cancer [21]. NMSC includes different types, such as Basal cell carcinoma (BCC), Squamous cell

carcinoma (SCC), Merkel cell carcinoma, Keratosis actinica, Pilomatrixal carcinoma, and Sebaceous carcinoma [8]. Sun exposure is known to be the key risk factor, as approximately 90% of non-melanoma skin cancer cases can be

Table 1 Summary of articles

Author, year	Location	Conditions	Research design	Number of patients (n)	Age	Main findings
Billa et al. [15]	France	Non-melanoma skin cancer	Prospective cohort	1427	43–51	Among HIV/HCV co-infected patients, non-melanoma skin cancer was the second most common non-HCV-liver cancer.
Chalouni et al. [16]	France	Non melanoma and melanoma skin cancer	Prospective cohort	548	49.5–56.6	Among HIV/HCV co-infected patients and HCV mono-infected patients, non-melanoma skin cancer was the most common non-HCV-liver cancer.
Ngoato et al. [18]	Tshwane	Hepatitis B virus infection in patients presenting for immunosuppressive cancer therapy	Cross sectional descriptive	107	50	Among HIV/HBV co-infected patients, Kaposi sarcoma was the third most common cancer.
Scheinfeld. [19]	United States	Pilomatrical carcinoma	Case Report	1	51	A 51-year-old male with HIV/HCV and hepatic cirrhosis presents with a 4 cm firm, purple nodule on the left upper limb that turns out to be pilomatrical carcinoma.
Dosal J, et al. [20]	United States	Multiple low-grade sarcomas of fibroblastic phenotype	Case Report	1	46	A 46-year-old white male with HIV, HCV, HBV, epidermodysplasia verruciformis, and anal carcinoma in situ presents with multiple asymptomatic, firm nodules on various body parts which are diagnosed as low-grade fibroblastic sarcomas.

attributed to UV radiation exposure, leading to the malignant alteration of keratinocytes [21].

Non-melanoma skin cancer (BCC, SCC)

A few studies have identified an association between NMSC and HIV/HCV patients, although the specific type of NMSC was not specified. For instance, a prospective study by Billa et al. examined patients co-infected with HIV and HCV [15]. Their analysis of non-AIDS-defining and non HCV-liver (NANL) related cancers revealed non-melanoma skin cancer as the second most frequent type, with 13 cases out of 60 total NANL cancers [15]. After adjusting for various factors in a final multivariable analysis, only age and the duration of HIV infection were significantly associated with a higher NANL cancer risk [15]. Other factors related to HCV infection, such as duration of infection, presence of cirrhosis, viral load, genotype, and viral response, showed no significant connection to cancer risk [15]. Therefore, this study suggests that in HIV/HCV co-infected individuals, age and a longer duration of HIV infection are the primary predictors of cancer risk, while factors specific to HCV infection appear to have minimal impact.

Another study by Chalouni et al. supports these findings [16]. Their research compared data from 548 HIV/HCV co-infected patients and 2016 HCV mono-infected patients [16]. Over a median follow-up of about 2–3 years, both groups developed similar numbers of NANL cancers, with the most common being non-melanoma skin cancer ($n=4$ for HIV/HCV co-infected and $n=5$ for HCV mono-infected patients). In addition, the next common cancer was melanoma ($n=2$) in HIV/HCV co-infected patients, while

melanoma was not reported in HCV mono-infected patients. Even though not specified in this study, NMSC usually refers to BCC and SCC [17]. While the case numbers may be relatively small, both studies suggest that NMSC is among the most common non-AIDS-defining (NANL) cancers in patients with HCV or HIV/HCV. They explain that chronic immunosuppression related to HIV co-infection could play a key role in the increased risk of these cancers.

Pilomatrical carcinoma

Pilomatrical carcinoma is a rare and aggressive form of NMSC, originating from the hair matrix cells. It is classified under adnexal tumors, which arise from the skin's adnexal structures such as hair follicles and sweat glands [22]. As a subtype of pilomatrixoma, it typically presents as a firm, painless swelling in the dermis, predominantly occurring on the head and neck [23]. This carcinoma is generally asymptomatic and can range in size from 1 to 10 cm [23]. Up to 2022, literature has documented approximately 130 reported cases, and one of those cases is reported as a case study by Scheinfeld of a patient with HIV/HCV [19, 24]. A 51-year-old male diagnosed with HIV in 1986 and living with HCV with hepatic cirrhosis presented with a 4-cm firm, purple nodule on the posterolateral aspect of his left upper limb, near the triceps muscle [19]. The nodule had been present for 9 months and gradually increased in size [19]. This case describes another example of an HIV/HCV co-infected patient developing a rare form of skin cancer [19].

Even though this is a single case report, it is important to note because pilomatrical carcinoma itself is an extremely rare malignancy, with fewer than 200 cases reported in the

literature, highlighting its significance in any new context [24]. In addition, the co-occurrence of HIV and HCV in this patient suggests that the immunosuppressive state induced by these chronic infections may predispose patients to develop rare skin cancers that are not typically associated with either HIV or HCV alone [19]. While pilomatrixal carcinoma is not an AIDS-defining cancer, the fact that it arose in a patient with dual viral co-infections points to the potential for co-infections to contribute to the emergence of uncommon malignancies in immunocompromised patients [24]. This case emphasizes the need for further investigation into the role of viral co-infections in the development of rare adnexal tumors and underscores the importance of vigilance in cancer screening for HIV/HCV co-infected individuals.

Sarcoma

Sarcomas are a diverse group of cancers that originate from connective tissues, including bone, muscle, fat, and cartilage [25]. These malignancies can occur in various parts of the body, including the skin, where they are considered a type of skin cancer due to their involvement of the skin's connective tissues [26]. Among different types of sarcomas, Kaposi sarcoma and Low-grade fibroblastic sarcoma have been reported with HIV infection with HCV and/or HBV [18, 20].

Kaposi sarcoma

Kaposi sarcoma (KS) is a rare cancer that manifests as malignant lesions on the skin, lymph nodes, mouth, and various internal organs [27]. Infection with Kaposi sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8), is a well-established risk factor for KS, though it is insufficient on its own to cause the disease [27]. While individuals infected with KSHV have a significantly higher risk of developing KS compared to the general population, the presence of the virus alone does not guarantee disease onset, indicating that additional factors play a crucial role in KS development [28].

A study by Ngoato et al. investigated cancer patients with and without HIV co-infection and found that Kaposi sarcoma (KS) was diagnosed exclusively in HIV-positive patients ($n=4$, 7.1%), making it the third most common cancer diagnosis among this group [18]. Notably, one of these patients ($n=1$, 25%) was also found to have occult HBV infection, suggesting that HBV may be present in a subset of KS cases in HIV-positive individuals [18].

Although the number of patients with KS, HIV, and HBV is small, this finding remains important [18]. The potential interplay between HBV, HIV, and immunosuppression in KS development raises the possibility that HBV may contribute

to the progression or susceptibility to KS in certain HIV-positive individuals. Furthermore, understanding this relationship could have clinical implications for the screening and management of co-infections in high-risk populations.

However, several limitations of the study should be acknowledged. The study population was predominantly female (96.3%, $n=103$), with ovarian cancer ($n=43$, 76.8%) and vulvar squamous cell carcinoma ($n=5$, 8.9%) as the most common diagnoses, which are cancers exclusive to females [18]. This introduces a significant gender bias, limiting the generalizability of the findings to male patients or those with non-gynecological cancers [18]. Moreover, the study did not specify the subtypes of KS diagnosed, an important distinction, as classic KS is not associated with HIV, while HIV-related KS is driven by immunosuppression [18].

Despite these limitations, the observation of occult HBV infection in a patient with both HIV and KS underscores the need for further research. Future studies should aim to explore the role of HBV in the development of KS in larger, more diverse populations, including males and patients with non-gynecological cancers, to better understand the complex interplay between HBV, HIV, and KS.

Low-grade fibroblastic sarcomas

Low-grade fibroblastic sarcomas are rare malignant tumors characterized by the presence of myofibroblasts [29]. These tumors are infrequent and their origin remains unclear. Typically, they are found in either bone or soft tissue and are most often observed in the head and neck regions, particularly affecting areas like the tongue and oral cavity [29]. Dorsal et al. documented a case involving a 46-year-old white male with a history of HIV, epidermodysplasia verruciformis, anal carcinoma in situ, and co-infection with both HCV and HBV [20]. The patient presented with multiple firm, asymptomatic nodules scattered across different parts of the body [20]. A biopsy of the nodules confirmed the presence of atypical spindle cell neoplasms consistent with low-grade fibroblastic sarcoma [20].

Although low-grade fibroblastic sarcomas are considered nonaggressive and have a low potential for metastasis, this particular case stands out for several reasons. Firstly, the occurrence of multiple lesions at different sites within the same patient is highly unusual for this type of sarcoma [29]. This raises intriguing questions about the possible interaction between the patient's long-standing HIV infection and the added complexity of co-infection with both HCV and HBV. The role of chronic immunosuppression in influencing the behavior of these neoplasms cannot be overlooked, as patients with HIV are known to be at higher risk for

developing malignancies, even those not typically considered AIDS-defining cancers.

What makes this case even more compelling is the fact that low-grade fibroblastic sarcomas are rarely reported in the context of any viral co-infection, let alone in an individual with triple viral involvement [20]. This suggests that the underlying viral milieu may play a role in the development or progression of these tumors in ways that are not yet fully understood. Although this is just a single case, it adds valuable insight into the potential for rare neoplastic processes to emerge in patients with HIV, HCV, and HBV co-infection, and underscores the need for ongoing research to better understand how these viruses may interact to influence tumorigenesis.

Discussion and conclusion

This systematic review compiled findings from multiple studies investigating skin cancers associated with co-infection of HIV and HCV and/or HBV. Notably, the majority of studies identified rare forms of skin cancer, such as adnexal (appendageal) skin cancers, pilomatrical carcinoma, Kaposi sarcoma (KS), and low-grade fibroblastic sarcomas, in co-infected patients. This review comes with several limitations that must be addressed. First, any statistical analysis of included papers was limited, largely due to the limited number of studies available for each skin cancer subtype and heterogeneity among the studies, with some focusing on non-AIDS/non-liver (NANL) cancers while others included AIDS-defining cancers such as KS. In addition, two of the studies were single case reports, which significantly limits the ability to draw broad conclusions [19, 20]. While these case reports, such as the one linking HIV/HCV/HBV co-infection with low-grade fibroblastic sarcoma, provide valuable insights, they should be interpreted cautiously and not be considered definitive evidence of an association between co-infection and these rare cancers [19, 20].

Despite these limitations, this review remains a significant first step in exploring the relationship between HIV, HBV, and HCV co-infection and skin cancer. It is the first systematic review to address this complex interplay, highlighting the need for more comprehensive research.

Even though co-infection of HIV/HCV or HIV/HBV is common as both viruses share similar modes of transmission, the management of HCV and/or HBV infection in the HIV-infected population poses a serious challenge for physicians [10, 30]. Approximately two-thirds of co-infected patients do not receive anti-HCV/HBV treatment for reasons such as poor compliance with highly active antiretroviral therapy (HAART), decompensated hepatic disease, active substance and alcohol use, and advanced HIV disease

[10, 30]. Thus, only a minority of such patients receive anti-HCV/HBV treatment [5, 10].

Despite ongoing research on various skin conditions of patients with HIV/HCV or HIV/HBV, the mechanism of interaction between these viruses is not well understood even for liver injury [10, 31]. However, successful control of HIV infection with HAART has been associated with reduced fibrosis progression and liver disease in co-infected patients [5]. Despite immune suppression, HCV-specific immune responses have been observed in co-infected patients, and the HCV viral load tends to be higher compared to HCV mono-infection, though its association with more severe liver injury remains uncertain due to the lack of an animal model for studying co-infection pathogenesis [31].

In conclusion, this systematic review highlights the rarity of skin cancers in the context of HIV/HCV and HIV/HBV co-infection and the critical need for further research. While the current data are limited by small sample sizes and case reports, this review serves as an important starting point for exploring these relationships. As more studies emerge, a deeper understanding of the interplay between these viral infections and skin cancer risk will help address key barriers to care and improve treatment outcomes for co-infected patients.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval All work reported in the paper has been performed by the authors, unless clearly specified in the text.

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Competing interests The authors declare no competing interests.

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