ORIGINAL CONTRIBUTION

Incidence Rate and Risk Factors for Anal Squamous Cell Carcinoma in a Cohort of People Living With HIV from 2004 to 2017: Implementation of a Screening Program

Yusnelkis Milanés Guisado, Ph.D.[1] • César Sotomayor, M.D.[1] • María Fontillón, Ph.D.[2]
Ana Domínguez Castaño, Ph.D.[3] • Nuria Espinosa, M.D., Ph.D.[1] • Cristina Roca, M.D.[1]
Luis F. López-Cortés, M.D., Ph.D.[1,4] • Pompeyo Viciana, M.D., Ph.D.[1]
Karin Neukam, Pharm.D., Ph.D.[1,4]

On behalf of the SeVIHanal Study Group
1 Servicio de Enfermedades Infecciosas, UCEIMP, Hospital Universitario Virgen del Rocío. Seville, Spain
2 Servicio de Anatomía Patológica, Hospital Universitario Virgen del Rocío. Seville, Spain
3 Servicio de Microbiología, UCEIMP, Hospital Universitario Virgen del Rocío. Seville, Spain
4 Instituto de Biomedicina de Sevilla/CSIC/Universidad de Sevilla, Seville, Spain

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BACKGROUND: Anal squamous cell carcinoma is rare, in general, but considerably higher in HIV-infected men who have sex with men. There is no consensus on the screening of at-risk populations.

OBJECTIVE: This study aimed to determine the incidence rates of anal squamous cell carcinoma and the efficacy of a screening program.

DESIGN: This is a cohort study (SeVIHanal/NCT03713229).

SETTING: This study was conducted at an HIV outpatient clinic in Seville, Spain.

PATIENTS: From 2004 to 2017, all patients with at least 1 follow-up visit were analyzed (follow-up group), including a subgroup of men who have sex with men who participated in a specialized program for screening and treating anal neoplasia (SCAN group) from 2011 onward.

MAIN OUTCOME MEASURES: The primary outcome measure was the incidence rate of anal squamous cell carcinoma.

RESULTS: Of the 3878 people living with HIV included in the follow-up group, 897 were transferred to the SCAN group; 1584 (41%) were men who have sex with men. Total follow-up was 29,228 person-years with an overall incidence rate for anal squamous cell carcinoma of 68.4/100,000 person-years (95% CI, 46.7–97.4). The changes in the incidence rate/100,000 person-years (95% CI) over time was 20.7 (3.40–80.5) for 2004 to 2006, 37.3 (13.4–87.3) for 2007 to 2010, and 97.8 (63.8–144.9) for 2011 to 2017 ($p < 0.001$). The strongest impact on the incidence of anal squamous cell carcinoma was made by the lack of immune restoration (adjusted incidence rate ratio (95% CI): 6.59 (4.24–10); $p < 0.001$), the Centers for Disease Control and Prevention category C (adjusted incidence rate ratio (95% CI): 7.49 (5.69–9.85); $p < 0.001$), and non-men who have sex with men (adjusted incidence rate ratio (95% CI): 0.07 (0.05–0.10); $p < 0.001$)

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Pompeyo Viciana and Karin Neukam are joint senior authors.

Correspondence: Karin Neukam, Pharm.D., Ph.D., Unit of Infectious Diseases, Clinical Microbiology and Preventive Medicine, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Avenida Manuel Siurot s/n. 41013. Sevilla, Spain. E-mail: karin.neukam@gmail.com

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in a Poisson analysis. From 2010 to 2017, incidence rates (95% CI) of anal squamous cell carcinoma within the SCAN group and the men who have sex with men of the follow-up group were 95.7 (39.6–202) and 201 (101–386)/100,000 person-years (adjusted incidence rate ratio (95% CI): 0.30 (0.23–0.39); $p<0.001$). The incidence rate ratio (95% CI) including non-men who have sex with men in the follow-up group was 0.87 (0.69–1.11); $p = 0.269$.

LIMITATIONS: Adherence to the visits could not be quantified.

CONCLUSION: Incidence rates of anal squamous cell carcinoma in people living with HIV increased significantly from 2004 to 2017, especially in men who have sex with men who were not being screened. Participation in the SCAN program significantly reduced the incidence of anal squamous cell carcinoma in men who have sex with men, in whom focus should be placed, especially on those presenting with Centers for Disease Control and Prevention category C and advanced immune suppression. See **Video Abstract** at http://links.lww.com/DCR/B734.

TASA DE INCIDENCIA Y FACTORES DE RIESGO DEL CARCINOMA ANAL A CÉLULAS ESCAMOSAS EN UNA COHORTE DE PERSONAS QUE VIVEN CON EL VIH DE 2004 A 2017: IMPLEMENTACIÓN DE UN PROGRAMA DE DETECCIÓN

ANTECEDENTES: El carcinoma anal a células escamosas es generalmente raro, pero considerablemente más alto en hombres infectados por el VIH que tienen relaciones sexuales con hombres. No hay consenso sobre el cribado de poblaciones en riesgo.

OBJETIVO: Este estudio tuvo como objetivo determinar las tasas de incidencia del carcinoma anal a células escamosas y la eficacia de un programa de detección.

DISEÑO: Estudio de cohorte (SeVIHanal / NCT03713229).

AJUSTE: Clínica ambulatoria de VIH en Sevilla, España.

PACIENTES: De 2004 a 2017, se analizaron todos los pacientes con al menos una visita de seguimiento (grupo F / U), incluido un subgrupo de hombres que tenían relaciones sexuales con hombres que participaron en un programa especializado de cribado y tratamiento de neoplasias anales (SCAN-group) a partir de 2011.

PRINCIPALES MEDIDAS DE RESULTADO: Tasas de incidencia del carcinoma anal a células escamosas.

RESULTADOS: De las 3878 personas que viven con el VIH incluidas en el grupo F / U, 897 fueron transferidas al grupo SCAN, 1584 (41%) eran hombres que tenían relaciones sexuales con hombres. El seguimiento total fue de 29228 personas-año con una tasa de incidencia general de carcinoma anal a células escamosas de 68,4 / 100000 personas-año [intervalo de confianza del 95%: 46,7-97,4]. El cambio en las tasas de incidencia / 100000 personas-año (intervalo de confianza del 95%) a lo largo del tiempo fue 20,7 (3,40-80,5) para 2004-2006, 37,3 (13,4-87,3) para 2007-2010 y 97,8 (63,8-144,9) para 2011-2017, p <0,001. El impacto más fuerte en la incidencia del carcinoma a células escamosas anal fue la falta de restauración inmunológica [índice de tasa de incidencia ajustado (intervalo de confianza del 95%): 6,59 (4,24-10); p <0,001], categoría C de los Centros de Control de Enfermedades [índice de tasa de incidencia ajustado (intervalo de confianza del 95%): 7,49 (5,69-9,85); p <0,001] y no hombres que tenían relaciones sexuales con hombres [razón de tasa de incidencia ajustada (intervalo de confianza del 95%): 0,07 (0,05-0,10); p <0,001] en el análisis de Poisson. Desde 2010-2017, las tasas de incidencia (intervalo de confianza del 95%) de carcinoma anal a células escamosas dentro del grupo SCAN y los hombres que tienen relaciones sexuales con hombres del grupo F / U fueron 95,7 (39,6-202) y 201 (101- 386) / 100000 personas-año [razón de tasa de incidencia ajustada (intervalo de confianza del 95%): 0,30 (0,23-0,39); p <0,001]. La razón de la tasa de incidencia (intervalo de confianza del 95%), incluidos los no hombres que tenían relaciones sexuales con hombres en F / U, fue de 0,87 [0,69-1,11); p = 0,269].

LIMITACIONES: No se pudo cuantificar la adherencia a las visitas.

CONCLUSIÓNES: La tasa de incidencia del carcinoma anal a células escamosas en personas que viven con el VIH aumentó significativamente de 2004 a 2017, especialmente en hombres que tenían relaciones sexuales con hombres que no se someten a pruebas de detección. La participación en el programa SCAN redujo significativamente la incidencia de carcinoma anal a células escamosas en hombres que tenían relaciones sexuales con hombres, en quienes se debe prestar una especial atención, sobre todo en aquellos que se presentan en la categoría C de los Centros de Control de Enfermedades con inmunodeficiencia avanzada. Consulte **Video Resumen** en http://links.lww.com/DCR/B734. (*Traducción—Dr. Xavier Delgadillo*)

KEY WORDS: Cancer of the anal canal; HIV infection; Men who have sex with men; Screening as prophylaxis; SeVIHanal; Squamous intraepithelial lesions.

Anal cancer is uncommon in the overall population, although an increasing trend has been observed in many countries.[1,2] Most of the invasive anal cancers are squamous cell carcinomas (SCCs), accounting for up to 90% of the cases.[3] Anal SCC is mainly caused by infection with high-risk human papillomavirus, especially genotypes 16 and 18[4] and is preceded by high-grade squamous intraepithelial lesions (HSIL).[5]

Human immunodeficiency virus-related immunosuppression represents another important risk factor for

the development of anal cancer,[6,7] along with receptive anal sex,[8] a widespread practice in HIV-infected men who have sex with men (MSM). Although in the non-HIV-infected, general population incidence rates (IRs) of less than 2 per 100,000 person-years (py) are commonly observed, IRs in HIV-negative MSM are 7-fold higher.[9] In people living with HIV (PLWH), IRs oscillate around 50 per 100,000 py[9–11] overall, and the presence of both risk factors for anal cancer results in IRs exceeding 100 per 100,000 py among HIV-infected MSM.[9,10] With the arrival and increasing use of highly active antiretroviral therapy (HAART) from 1996 onward, life expectancy of the HIV-infected population increased, resulting in a shift in cause of death. In this context, non-AIDS defining cancers have gained importance, among them, anal SCC.[1,2]

A rise in anal SCC IRs was observed in the early HAART era,[10,11] whereas there is evidence that no further increase has occurred from the later HAART years to the present.[12] This study aimed to analyze the development of anal SCC incidence in the HAART era in PLWH, as well as to determine the impact of a specialized screening program for anal neoplasia under real-life conditions.

PATIENTS AND METHODS

Study Population

The study was conducted at the Unit of Infectious Diseases of the Virgen del Rocío University Hospital in Seville, Southern Spain where PLWH are seen on a regular basis following a cohort protocol begun in 2004, and clinical and epidemiological data are prospectively entered in electronic medical records (ACyH1, Betek 43 SL, Spain). All patients who had at least 1 follow-up visit were included in the analysis (F/U group). In September 2010, a specialized program for screening and treating anal neoplasia (SCAN) was established for MSM within the Seville Cohort of People Living with HIV at Risk for Anal Cancer (SeVIHanal Cohort, clinicaltrials.gov: NCT03713229), which includes anal liquid cytology, high-resolution anoscopy (HRA), and thermocoagulation in those with confirmed histological HSIL, as described previously.[13] All MSM were invited to attend the program and thus follow the SCAN protocol, and, on consent, the participation in the F/U group was stopped, subjects were transferred and referred to as the SCAN group, while the time of switch with the correspondent clinical parameters was considered the baseline visit within SCAN.

Definition of Clinical Parameters

All cases of anal cancer analyzed in this study had biopsy-proven anal SCC stage 1 or higher, as defined by the National Cancer Institute of the National Institutes of Health, US Department of Health and Human Services (www.cancer.gov). Adenocarcinoma and other cancers were excluded.

Immune restoration (ImR) was defined as a recovery of a CD4+ T-cell count to 650 cells/μL or more in patients who presented a baseline CD4+ T-cell count of less than 600 cells/μL.

The clinical stage of HIV infection was classified into 3 categories according to the definitions of the Centers for Disease Control and Prevention (CDC),[14] which are summed as follows: Category A, asymptomatic chronic HIV infection or acute infection; category B, symptomatic conditions attributable to HIV infection that have a clinical course or require management that is complicated by HIV infection; category C, clinical conditions listed in the AIDS surveillance case definition. Once a category C condition has occurred, the person will remain in category C.

The presence of sexually transmitted diseases (STDs) was considered when gonorrhea, chlamydia, or syphilis were diagnosed within 12 months before or at baseline.

Statistical Analysis

Descriptive statistics of demographic factors and baseline HIV infection status were conducted for the study population. The outcome variable was the diagnosis of anal SCC throughout the whole study period, which was then divided into two 7-year periods (2004–2010 vs 2011–2017), where the cutoff date (December 31, 2010) marks the launching date of the SCAN program, and the second period defines the time span to evaluate SCAN. Both periods were further divided into prespecified periods of 3 and 4 years, where the longer periods (2004–2007 and 2010–2014) were scheduled first to provide similar numbers of PLWH in each, because an increase of participants over time could be expected after starting both the cohort protocol within the routine follow-up, as well as the SCAN program. To compare the F/U group with the SCAN group, clinical parameters at the first visit in 2011 were set as baseline values in PLWH who had a baseline visit before 2011 within the F/U group. These patients together with those who were included in the F/U group in 2011 or later formed the evaluation subgroup ($F/U_{2014–2017}$ group) within the F/U group. Incidence rates and IR ratios (IRRs) with 95% CIs of SCC were calculated and expressed as cases per 100,000 py. Poisson regression models with log-linear function were developed to estimate IRRs and to compare SCC risk within PLWH. The model was adjusted by all factors with a significance level of $p < 0.2$ in the univariate models. Standard errors estimated via a robust variance estimator were used. Statistical analyses were performed by means of the SPSS statistical software package release 23.0 (IBM Corporation, Somers, NY) and R Statistical Software (Foundation for Statistical Computing, Vienna, Austria).

Ethics Approval and Consent to Participate

The study was designed and performed according to the Declaration of Helsinki and was approved by the

Ethics Committee of the Virgen del Rocío University Hospital (Seville, Spain; Ref 03/2006). All patients gave their written informed consent both to be included in the database and to allow the use of their anonymized data, photographs, or videoscopies for scientific research and HRA training programs, thereby ensuring the protection of personal data in accordance with the Spanish Personal Data Protection Organic Law15/199 enacted on December 13, 1999.

RESULTS

Study Population

From January 2004 to December 2017, a total of 3878 of 4087 (95%) PLWH followed in the clinic were eligible for the present study. Median (interquartile range) age at the moment of inclusion was 38 (32–44) years, 1584 (40.8%) were MSM and 673 (17.4%) were women. A total of 2952 (76.1%) PLWH presented a baseline $CD4^+$ T-cell count of <600 cells/μL. Immune restoration was observed in 924 of 1204 PLWH with a baseline $CD4^+$ T-cell count of 350 to 600 cells/μL and 727 of 1748 PLWH with a baseline $CD4^+$ T-cell count less than 350 cells/μL. Respective numbers for MSM were 502 of 584 MSM for 350 to 600 cells/μL and 316 of 582 MSM for <350 cells/μL. The median (interquartile range) time to immune recuperation was 20 (6.5–51) months. Table 1 shows detailed baseline characteristics of the study groups.

Cases of Anal SCC

During the study period, a total of 20 anal SCCs were diagnosed, accounting for a rate of 1.5 cases per year. Eleven (55%) of the patients were MSM; the remaining were heterosexual male injecting drug users. The distribution per calendar year is displayed in Figure 1. Four of the 20 anal SCCs were diagnosed within the SCAN group. Of these, 2 (50%) each were T1 or T2, without spread to nearby lymph nodes or distant sites. For all anal SCCs, TNM staging according to the American Joint Committee on Cancer and the Union for International Cancer Control, 8th edition (2017), is presented in Table 2, along with patient characteristics. Two of the 4 patients with anal SCC in the SCAN group were adherent to their scheduled visits and were asymptomatic at the time of diagnosis, whereas the other 2 did not attend the scheduled visits and were diagnosed when they presented because of symptoms.

IR and IRR of Anal SCC

Total follow-up was 29,228 py, resulting in an overall IR (95% CI) of 63.9 (41.7–94.6) per 100,000 py. The IRR (95% CI) of anal SCC comparing 2011 to 2017 versus 2004 to 2010 was 3.15 (1.16–10.9), $p<0.001$. The corresponding IRs of anal SCC according to the calendar year of patient inclusion are shown in Figure 2A.

The proportions of MSM who entered this study increased from 24.2% in 2004 to 2006 to 48.4% in 2007 to 2010, 66.7% in 2011 to 2014, and 70.4% in 2015 to 2017 ($p_{\text{linear association}} < 0.001$). The IR of anal SCC in the subgroup

TABLE 1. Characteristics of the study groups and subgroups at enrollment and the beginning of the subanalyses

Parameter	*SCAN group (n = 897)*	*F/U group (n = 3878)*	*p value*[a]	*MSM (n = 1584)*	*p value*[a]	*F/U$_{2011\text{-}2017}$ (n = 3206)*	*p value*[a]
Age, y	39 (31–47)	38 (33–44)	<0.001	35 (29–43)	<0.001	42 (33–47)	<0.001
Male sex, n (%)	897 (100)	3205 (83)	<0.001	1584 (100)		2655 (83)	<0.001
HIV transmission route, n (%)			<0.001				<0.001
MSM	897 (100)	1584 (41)		1584 (100)		1457 (45)	
IDU	0	1271 (33)		0		880 (27)	
Heterosexual	0	826 (21)		0		721 (23)	
Other	0	197 (5.1)		0		148 (4.6)	
Level of education, n (%)[b]			<0.001		0.277		<0.001
Low	72 (8.1)	1581 (43)		150 (9.7)		1163 (38)	
Medium	736 (83)	1917 (52)		1280 (83)		1723 (57)	
High	79 (9)	159 (4.3)		119 (7.7)		145 (4.8)	
Tobacco use, n (%)	372 (42)	1851 (48)	0.001	735 (46)	0.18	1513 (47)	0.002
CDC category, n (%)			<0.001		<0.001		<0.001
A	728 (81)	3308 (85)		1437 (91)		2782 (87)	
B	86 (9.6)	137 (3.5)		36 (2.3)		102 (3.2)	
C	80 (9.3)	433 (11)		111 (7)		322 (10)	
HIV-RNA <200 copies/mL, n (%)	667 (74)	1208 (32)	<0.001	311 (20)	<0.001	1716 (54)	<0.001
$CD4^+$ T-cell count, cells/μL[c]	592 (450-778)	391 (214-592)	0.081	431 (267-614)	<0.001	479 (308-665)	<0.001
$CD4^+$ T-cell nadir, cells/μL[c]	294 (186-418)	198 (75-323)	<0.001	279 (157-406)	0.034	230 (102-388)	<0.001
Baseline STD, n (%)	110 (12)	211 (5.4)	<0.001	190 (12)	0.844	186 (5.8)	<0.001

CDC = Centers for Disease Control and Prevention; F/U = follow-up; IDU = injecting drug users; MSM = men who have sex with men; SCAN = screening and treating anal neoplasia; STD = sexually transmitted disease.

[a]As compared with the SCAN group.

[b]Low: primary/no school; medium: secondary school; high: university degree; available in 3630 patients.

[c]Median (interquartile range).

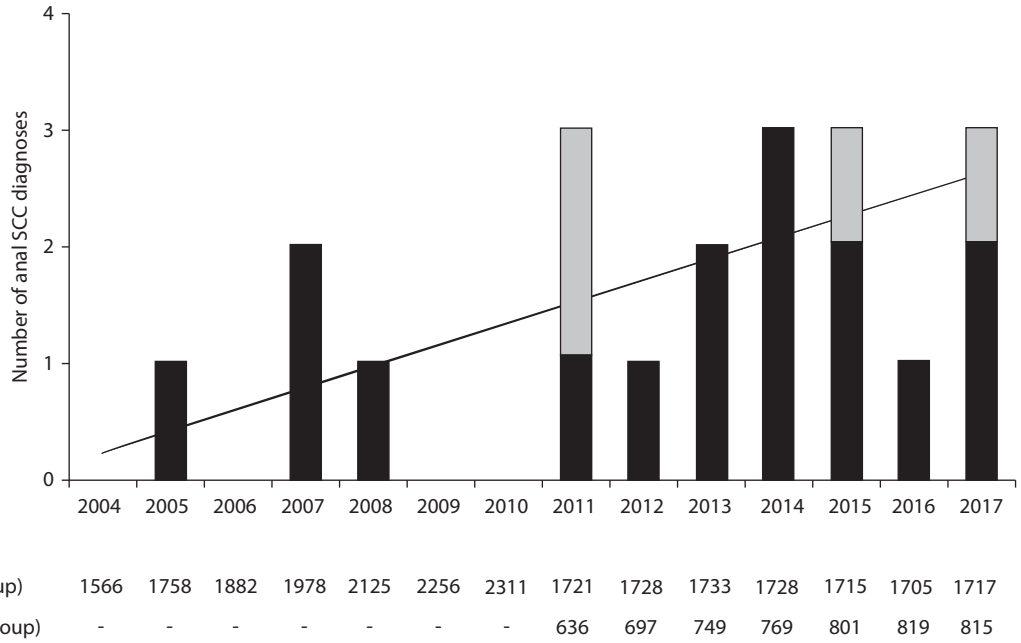

FIGURE 1. Number of anal squamous cell carcinoma (SCC) observed cases by calendar year (black bars: F/U group; gray bars: SCAN group; black line: trend line for overall numbers, slope = 0.185). F/U = follow-up; SCAN = screening and treating anal neoplasia.

of MSM was 103.6 (61.6–166) per 100,000 py, with an accumulated follow-up of 10,614 py. The change in the IR over time is displayed in Figure 2B.

For the non-MSM population, follow-up was 18,613 py. The overall IR was 48.4 (27.2–81.0) per 100,000 py. The change in the IR over time is shown in Figure 2C.

Risk Factors for Anal SCC

Poisson regression models identified several factors associated with anal SCC in the overall population. An age younger than 35 years (adjusted (a) IRR (95% CI): 0.42 (0.29–0.62); $p < 0.001$) or older than 50 years (aIRR (95% CI): 0.31 (0.18–0.52); $p < 0.001$), a high level of education (aIRR

TABLE 2. Characteristics of the patients who developed anal cancer at the time of diagnosis

Study group	*Stage*	*Cancer site*	*Nadir*	*HIV-RNA (copies/mL)*	*Age, y*	*Tobacco use*	*Time last visit, mo*	*DRE*	*Symptoms*
SCAN	T2N0M0 (IIA)	Anal canal	155	<50	57	Yes	8	Normal	Diarrhea, bleeding
SCAN	T1N0M0 (I)	Anal canal	127	281	50	Yes	1	Normal	Anal pain, weight lost
SCAN	T1N0M0 (I)	Anal canal	308	<20	54	No	11	Lump and indurated nodule	Anal ulcer, tenderness, serohematic discharge
SCAN	T2N0M0 (IIA)	Anal canal	316	<20	50	Yes	60	Lump	Indurated anal nodule
F/U	T4b N1M0 (IIIC)	Anal canal	210	<20	62	No	12	Lump	Bleeding
F/U	T2N0M0 (IIA)	Anal canal	58	<20	54	Yes	24	Lump and indurated nodule	Hematic discharge, fistula
F/U	T3N1aM0 (IIIC)	Perianal	174	63	46	No	1	Condyloma	Anal pain
F/U	T3N1aM0 (IIIC)	Anal canal	1	<20	37	Yes	12	Condyloma	Anal tenderness
F/U	T3N0M0 (IIB)	Anal canal	543	<20	59	No	2	Condyloma	Anal pain, bleeding
F/U	T4N1aM0 (IIIC)	Anal canal	14	177	27	Yes	5	Condyloma	Anal pain, bleeding
F/U	T4N1cM1 (IV)	Anal canal	101	294	39	Yes	53	Condyloma	Abscess, tenderness, fever
F/U	T1N0M0 (I)	Perianal	25	<20	44	Yes	31	Condyloma fistula	Anal tenderness, serohematic discharge
F/U	T4N1aM0 (IIIC)	Anal canal	30	<20	56	Yes	1	Normal	Diarrhea, bleeding, weight loss
F/U	T2N1bM0 (IIIA)	Anal canal	8	81300	39	Yes	1	Abscess	Abscess, tenderness, fever
F/U	T3N1cM1 (IV)	Anal canal	66	408	47	Yes	24	Condyloma	Condyloma
F/U	T4N0M0 (IIIB)	Anal canal	89	<20	48	Yes	12	Condyloma	Condyloma
F/U	T4N1cM0 (IIIC)	Anal canal	48	<20	49	Yes	1	Normal	Constipation, bleeding, pain
F/U	T4N1cM0 (IIIC)	Anal canal	354	<20	50	Yes	24	Condyloma	Abscess, tenderness, fever
F/U	T1N0M0 (I)	Anal canal	ND	ND	60	ND	ND	Normal	Anal pain
F/U	T4N1cM0 (IIIC)	Anal canal	ND	ND	46	Yes	12	Condyloma	Anal pain, bleeding

Time last visit = time from last clinical visit to diagnosis; DRE = digital rectal examination result; F/U = follow-up; ND = not done; SCAN = screening and treating anal neoplasia.

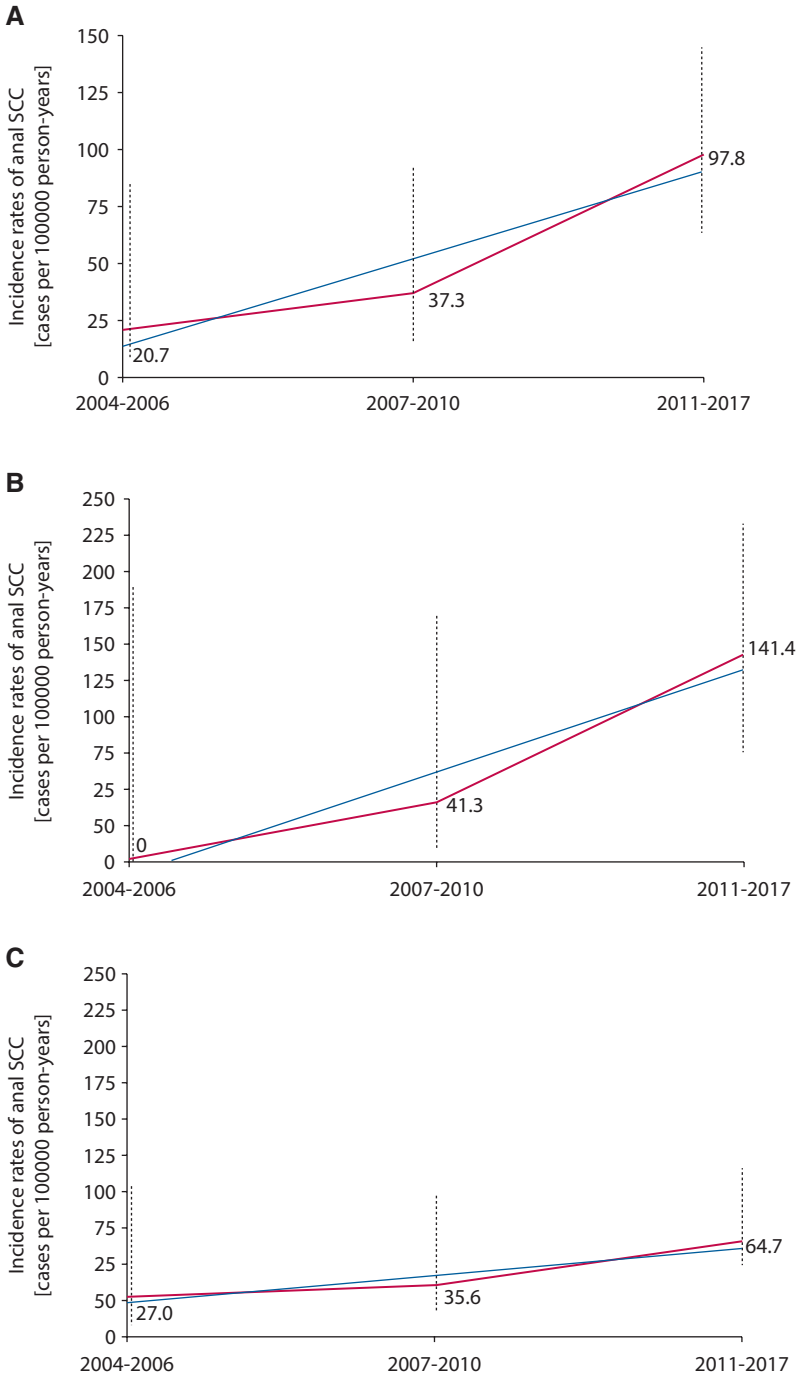

FIGURE 2. Incidence rates (95% CI: vertical line) of anal squamous cell carcinoma (SCC) in the overall population (A), men who have sex with men (MSM) (B), and non-MSM (C). Solid line: incidence rate over time; dashed line: linear trend.

(95% CI): 0.32 (0.23–0.46); $p < 0.001$), as well as injecting drug use as transmission route compared with having sex with men (aIRR (95% CI): 0.07 (0.05–0.1); $p < 0.001$) was protective for SCC. A negative impact was observed among PLWH with a baseline $CD4^+$ T-cell count of 350 to 600 or <350 cells/μL who did not achieve ImR (aIRR (95% CI): 2.89 (1.80–5); $p < 0.001$ and aIRR (95% CI): 6.59 (4.24–10); $p < 0.001$). Likewise, CDC category C at baseline (aIRR (95% CI): 7.49 (5.69–9.85); $p < 0.001$), the inclusion period from 2011 to 2017 (aIRR (95% CI): 3.02 (2.2–4.15); $p < 0.001$), and tobacco use 2.68 (1.92–3.76) showed an independent, negative impact on the incidence of anal SCC. All unadjusted and adjusted IRRs for the potential predictors for anal SCC analyzed are displayed in Table 3.

Among MSM, the factors associated with the incidence of anal SCC in MSM showed a trend similar to those

TABLE 3. Incidence rates and incidence rate ratios of anal SCC in the overall population of PLWH and in the subgroup of MSM throughout the study period (2004–2017)

Risk Factor	*Person-years*	*Observed anal SCC*	*IR[a] (95% CI) per 100,000 py*	*Unadjusted IRR[a] (95% CI)*	*p value*	*Adjusted IRR[a] (95% CI)*	*p value*
All PLWH							
Overall	29,228	20	68.4 (46.7–97.4)				
Age, y							
<35	9099	4	43.9 (18.2–92.8)	0.73 (0.51–1.02)	0.066	0.42 (0.29–0.62)	<0.001
35–50	17,405	14	80.4 (50.9–122)	Ref.		Ref.	
>50	2723	2	73.5 (20.7–203)	0.23 (0.16–0.32)	<0.001	0.31 (0.18–0.52)	<0.001
Level of education[b]							
Low/without studies	15,683	14	89.3 (56.5–136)	Ref.		Ref.	
Medium	7121	3	42.1 (15.1–98.7)	0.34 (0.28–0.53)	<0.001	0.24 (0.16–0.36)	<0.001
High	4645	3	64.6 (23.2–151)	0.78 (0.59–1.04)	0.086	0.32 (0.23–0.46)	<0.001
Risk group							
MSM	10,614	11	103 (61.6–166)	Ref.		Ref.	
Male IDU/others	13,356	9	67.4 (37.9–113)	0.50 (0.40–0.61)	<0.001	0.07 (0.05–0.1)	<0.001
Female	5257	0	0	0	–	0	–
Study group							
SCAN	4181	4	95.7 (39.6–202)	1.49 (0.43–4.08)	0.319		
F/U	25,046	16	63.9 (41.7–94.6)	Ref.			
Calendar year							
2004–2006	4828	1	20.7 (3.40–80.5)	Ref.		Ref.	
2007–2010	8048	3	37.3 (13.4–87.3)	1.80 (0.23–36.4)	<0.001	1.79 (0.81–2.3)	0.025
2011–2017	16,352	16	97.8 (63.8–145)	4.72 (0.96–85.3)	<0.001	3.02 (2.2–4.15)	<0.001
Tobacco use							
Yes	16,563	13	78.5 (48.7–121)	1.42 (1.15–1.76)	0.001	2.68 (1.92–3.76)	<0.001
No	12,664	7	55.3 (28.6–98.6)	Ref.		Ref.	
CDC category							
C	6047	11	182 (108–291)	4.65 (3.54–6.00)	<0.001	7.49 (5.69–9.85)	<0.001
A or B	23,180	9	38.8 (18.7–39.5)	Ref.		Ref.	
ImR during follow-up							
No ImR, BL <350	5268	10	190 (111–310)	3.55 (2.61–4.83)	<0.001	6.59 (4.24–10)	<0.001
ImR, BL <350 cells	6536	2	30.6 (8.6–84.5)	1.03 (0.71–1.51)	0.544	0.96 (0.59–1.58)	0.879
No ImR, BL 350–600	1318	1	75.9 (12.5–295)	1.21 (0.66–2.20)	0.858	2.89 (1.80–5)	<0.001
ImR, BL 350–600	8002	5	62.5 (28.5–123)	2.33 (1.71–3.17)	<0.001	2.0 (1.32–3.07)	0.001
BL >600	7954	2	25.1 (7.1–69.4)	Ref.		Ref.	
HIV RNA ≥200 copies/mL							
≥25% during follow-up	9730	7	71.9 (37.3–128)	1.08 (0.87–1.33)	0.491		
<25% during follow-up	19,497	13	66.7 (41.4–101)	Ref.			
Baseline STD	21,140						
Yes	2659	1	37.6 (6.2–146)	0.81 (0.55–1.19)	0.278		
No	26,431	19	71.9 (48.6–103)	Ref.			
MSM							
Overall	10,614	11	103.6 (61.6–166)				
Age, y							
<35	4364	2	45.8 (12.9–127)	0.12 (0.07–0.20)	<0.001	0.89 (0.74–1.08)	0.236
35–50	5018	8	159 (86.3–275)	Ref.		Ref.	
>50	1230	1	81.3 (13.3–316)	0.66 (0.40–0.97)	0.038	0.39 (2.45–0.62)	<0.001
Level of education[b]							
Low/without studies	2509	6	240 (118–446)	Ref.		Ref.	
Medium	3685	3	81.5 (29.3–191)	0.22 (0.15–0.33)	<0.001	0.93 (0.72–1.20)	0.586
High	3761	2	53.2 (15.0–147)	0.29 (0.20–0.41)	<0.001	1.14 (0.89–1.44)	0.287
Study group							
SCAN	4181	4	95.7 (39.6–202)	0.88 (0.18–3.46)	0.878		
F/U	6439	7	109 (56–194)	Ref.			
Calendar year							
2004–2006	1119	0	0 (0.0–168)	Ref.		Ref.	
2007–2010	2422	1	41.3 (6.8–161)	0.92 (0.09–19.9)	<0.001	1.06 (0.57–1.97)	0.863
2011–2014	3691	4	108 (44.9–229)	1.52 (0.24–29.0)	<0.001	1.34 (0.24–3.08)	<0.001
2015–2017	3382	6	177 (86.9–330)	2.32 (0.41–43.3)	<0.001	2.01 (1.78–5.05)	0.035

(*Continued*)

TABLE 3. Continued

Risk Factor	Person-years	Observed anal SCC	IR[a] (95% CI) per 100,000 py	Unadjusted IRR[a] (95% CI)	p value	Adjusted IRR[a] (95% CI)	p value
Tobacco use							
Yes	4854	8	165 (89.3–284)	4.40 (3.09–6.27)	<0.001	1.54 (1.28–1.86)	<0.001
No	5753	3	52.15 (18.7–122)	Ref.		Ref.	
CDC category							
C	1054	6	570 (280–1062)	13.2 (10.1–17.4)	<0.001	1.15 (0.84–1.58)	0.379
A or B	9569	5	52.3 (23.9–101)	Ref.		Ref.	
ImR during follow-up							
No ImR, BL <350	1159	4	344 (143–727)	2.89 (1.91–4.38)	<0.001	1.78 (1.09–2.20)	0.014
ImR, BL <350	2401	1	41.6 (6.83–162)	0.65 (0.40–1.08)	0.097	1.67 (1.32–2.02)	<0.001
No ImR, BL 350–600	331	1	303 (49.6–1177)	2.09 (1.04–4.21)	0.038	1.1 (0.12–1.20)	0.099
ImR, BL 350–600	3626	3	82.7 (29.7–194)	1.15 (0.78–1.71)	0.476	0.40 (0.26–0.78)	0.235
BL >600	3097	2	64.6 (18.2–178)	Ref.		Ref.	
HIV RNA ≥200 copies/mL							
≥25% during follow-up	3024	4	132 (54.8–280)	1.02 (0.74–1.42)	0.889		
<25% during follow-up	7590	7	92.3 (45.8–165)	Ref.			
Baseline STD							
Yes	2122	1	47.1 (7.73–183)	Ref.			
No	8423	10	119 (68.8–194)	0.55 (0.16–1.58)	0.254		

BL = baseline; CDC = Centers for Disease Control and Prevention; F/U = follow-up; IDU = injecting drug users; ImR = immune restoration of $CD4^+$ T cells according to baseline $CD4^+$ T-cell count in cells/μL; IR = incidence rate; IRR = incidence rate ratio; MSM = men who have sex with men; PLWH = people living with HIV; SCAN = screening and treating anal neoplasia; SCC = squamous cell carcinoma; STD = sexually transmitted diseases; py = person-years.
[a]IRR and *p* values are from a Poisson regression model.
[b]Low: primary/no school; medium: secondary school; high: university degree.

identified in the overall population, although statistical significance was not reached in some settings such as age younger than 35 years (aIRR (95% CI): 0.89 (0.74–1.08); $p = 0.236$), CDC category C (aIRR (95% CI): 1.15 (0.84–1.58); $p = 0.379$), and no ImR in MSM with a $CD4^+$ T-cell count of 350 to 600 cells/μL at baseline (aIRR (95% CI): 1.10 (0.12–1.20); $p = 0.099$; Table 4).

Evaluation of the Screening Program (2011–2017)

Of the 3878 PLWH included in the F/U group, 672 stopped clinical follow-up before 2011. The remaining 3206 PLWH formed the $F/U_{2011–2017}$ subgroup, including 1457 (45%) MSM (Table 1). A total of 897 MSM started the screening program between 2011 and 2017 and were transferred to the SCAN group. Accumulated follow-up was 4181 py for

TABLE 4. Incidence rates and incidence rate ratios of anal (SCC) in the overall population of PLWH and in the subgroup of MSM during the SCAN evaluation period (2011-2017).

Risk Factor	Person-years	Observed anal SCC	IR[a] (95% CI) per 100,000 py	Unadjusted IRR[a] (95% CI)	p value	Adjusted IRR[a] (95% CI)	p value
PLWH							
Overall	16,352	16	97.8 (63.8–145)				
Age, y							
<35	4017	3	74.7 (26.8–175)	0.36 (0.25–0.52)	<0.001	0.86 (0.60–1.23)	0.397
35–50	9988	11	110 (65.4–176)	Ref.			
>50	2346	2	85.3 (24.0–235)	0.87 (0.63–1.18)	0.365	0.76 (0.56–1.03)	0.073
Level of education[b]							
Low/without studies	8126	11	135.4 (80.5–216)	Ref.		Ref.	
Medium	4296	3	69.8 (25.1–164)	0.52 (0.38–0.70)	0.003	0.52 (0.38–0.70)	<0.001
High	3024	2	66.1 (18.6–183)	0.61 (0.44–0.84)	<0.001	0.39 (0.28–0.54)	<0.001
Risk group							
MSM	7073	10	141.4 (81.9–231)	Ref.		Ref.	
Male IDU/others	6486	6	92.5 (45.4–172)	0.55 (0.44–0.69)	<0.001	0.07 (0.05–0.09)	<0.001
Female	2825	0	0	0	–	0	–
Study group							
SCAN	4181	4	95.7 (39.6–202)	0.87 (0.69–1.11)	0.269		
$F/U_{2011–2017}$	12,171	12	98.6 (60–155)	Ref.			

(*Continued*)

TABLE 4. Continued

Risk Factor	*Person-years*	*Observed anal SCC*	*IR[a] (95% CI) per 100,000 py*	*Unadjusted IRR[a] (95% CI)*	*p value*	*Adjusted IRR[a] (95% CI)*	*p value*
Calendar year							
2011–2014	6857	9	97.6 (54.9–164)	0.92 (0.77–1.11)	0.394		
2015–2017	9404	7	98.2 (50.9–17)	Ref.			
Tobacco use							
Yes	8641	9	107.8 (60.5–180)	1.96 (1.46–2.62)	<0.001	2.16 (1.65–2.83)	<0.001
No	7710	7	87.5 (45.3–156)	Ref.		Ref.	
CDC category							
C	3480	10	287.4 (166.5–469)	9.12 (7.22–11.5)	<0.001	12.2 (9.36–15.8)	<0.001
A or B	12,867	6	46.6 (22.9–86.8)	Ref.		Ref.	
ImR during follow-up							
No ImR, BL <350	2372	6	253 (124–471)	2.1 (1.67–2.63)	<0.001	2.07 (1.57–2.73)	<0.001
ImR, BL <350 cells	1912	0	–	–	–	–	–
No ImR, BL 350–600	1148	0	–	–	–	–	–
ImR, BL 350–600	5024	2	39.8 (11.2–110)	0.25 (0.17–0.36)	<0.001	0.35 (0.25–0.50)	<0.001
BL >600	5862	7	119 (61.9–213)	Ref.		Ref.	
HIV RNA ≥200 copies/mL							
≥25% of follow-up	4524	6	154.7 (80.2–276)	1.27 (1.00–1.62)	0.048	1.23 (0.94–1.62)	0.133
<25% of follow-up	11,816	10	76.2 (42.8–128)	Ref.		Ref.	
Baseline STD							
Yes	590	1	169.5 (27.8–659)	1.76 (1.10–2.79)	0.017	1.29 (0.83–1.99)	0.259
No	15,757	15	95.2 (61.2–143)	Ref.		Ref.	
MSM							
Overall	7073	10	141.4 (81.9–231)				
Age, y							
<35	2771	2	72.2 (20.4–199)	0.31 (0.20–0.48)	<0.001	0.86 (0.61–1.21)	0.236
35–50	3378	6	177.6 (87–331)	Ref.		Ref.	
>50	924	2	216.5 (61–598)	1.35 (0.92–1.98)	0.127	1.04 (0.74–1.37)	0.974
Level of education[b]							
Low/without studies	1629	5	368.3 (180–686)	Ref.		Ref.	
Medium	2688	3	111.6 (40–261)	0.29 (0.19–0.43)	<0.001	0.25 (0.19–0.34)	<0.001
High	2566	2	77.9 (30–215)	0.33 (0.23–0.49)	<0.001	0.31 (0.23–0.43)	<0.001
Study group							
SCAN	4181	4	95.7 (39.6–202)	0.41 (0.38–0.45)	<0.001	0.3 (0.23–0.39)	<0.001
$F/U_{2011–2017}$	2892	6	201 (101–386)	Ref.		Ref.	
Calendar year							
2011–2014	3691	4	108 (44.9–229)	Ref.		Ref.	
2015–2017	3382	6	177 (86.9–330)	1.40 (1.08–1.81)	0.011	2.45 (1.9–3.17)	<0.001
Tobacco use							
Yes	2771	7	252.6 (130–451)	4.35 (2.78–6.82)	<0.001	3.4 (2.54–4.57)	<0.001
No	4301	3	69.8 (25–163)	Ref.		Ref.	
CDC category							
C	742	6	808.6 (396–1506)	17.5 (12.9–23.7)	<0.001	10.8 (8.33–13.9)	<0.001
A or B	6331	4	63.2 (26.2–134)	Ref.		Ref.	
ImR during follow-up							
No ImR, BL <350	614	4	651 (269–1376)	2.81 (2.07–3.82)	<0.001	2.45 (1.89–3.17)	<0.001
ImR, BL <350 cells	923	0					
No ImR, BL 350–600	332	0					
ImR, BL 350–600	2577	1	38.8 (6.38–151)	0.07 (0.03–0.14)	<0.001	0.03 (0.02–0.05)	<0.001
BL >600	2616	5	191 (87.3–376)	Ref.		Ref.	
HIV RNA ≥200 copies/mL							
≥25% of follow-up	2026	3	148 (53.2–347)	0.66 (0.16–2.77)	0.571		
<25% of follow-up	5045	7	138 (71.9–247)	Ref.			
Baseline STD							
Yes	503	1	198 (32.6–773)	1.34 (0.78–2.31)	0.293		
No	6570	9	136 (76.9–229)	Ref.			

BL = baseline; CDC = Centers for Disease Control and Prevention; F/U = follow-up; IDU = injecting drug users; ImR = immune restoration of $CD4^+$ T cells according to baseline $CD4^+$ T-cell count in cells/μL; IR = incidence rate; IRR = incidence rate ratio; MSM = men who have sex with men; PLWH = people living with HIV; CAN = screening and treating anal neoplasia; SCC = squamous cell carcinoma; STD = sexually transmitted diseases; py = person-years.

[a]IRR and *p* values are from a Poisson regression model.

[b]Low: primary/no school; medium: secondary school; high: university degree.

the SCAN group and 2892 py for MSM of the $F/U_{2011–2017}$ subgroup. In the SCAN group, the IRs (95% CI) were 100 (28.3–277) and 95.7 (26.9–264) per 100,000 py for 2011 to 2014 and 2015 to 2017 (p = 0.378). Corresponding numbers for MSM in the $F/U_{2011–2017}$ subgroup were 167.5 (60.1–392) and 157.3 (56.5–368.3) per 100,000 py (p = 0.939). Incidence rates and IRRs analyzing SCAN versus $F/U_{2011–2017}$ during different periods are shown in Table 5. The multivariate Poisson regression model revealed an aIRR (95% CI) of 0.3 (0.23–0.39; $p < 0.001$) for the SCAN group versus MSM of the $F/U_{2011–2017}$ subgroup during the evaluation period (Table 4). As observed in the overall PWLH population, the inclusion period 2015 to 2017 (aIRR (95% CI): 2.45 (1.9–3.17); $p < 0.001$), CDC category C (aIRR (95% CI): 10.8 (8.33–13.9); $p<0.001$), and a baseline $CD4^+$ T-cell count of <350 cells/μL without achieving ImR (aIRR (95% CI): 2.45 (1.89–3.17); $p < 0.001$) were among the factors that had an impact on the incidence of anal SCC. The complete analysis is shown in Table 4.

DISCUSSION

The present study reveals a significant increase in the incidence of anal SCC from 2004 to 2017 in a cohort of almost 4000 PLWH. The SCAN program was implemented to detect and treat pre-stages of anal SCC, and the present data show that SCAN significantly reduces the incidence of anal SCC in MSM.

Many studies focus on the detection of HSIL, but less is known about the current prevalence of anal SCC among the non-AIDS-defining cancers. The overall IR of anal SCC was 68 per 100,000 py in this cohort of PLWH, which is within the range of 60 to 69 per 100,000 py reported from large cohorts such as MACS[11] and NA-ACCORD.[15] However, MACS and NA-ACCORD data do not include the last decade and various reports describe increases in anal SCC after the early HAART era,[9,11,12,16–18] which then plateaued or even decreased.[12,18,19] Although an increasing trend in anal SCC was observed through 2007 in many countries, Spain was not among them.[2] Although the IR of anal SCC was low from 2004 to 2006 in the present work, it almost doubled to 37 per 100,000 py from 2007 to 2010 and reached almost 100 per 100,000 py from 2011 to 2017. It is important to note that, when only MSM were considered, a significant increase over time was also observed throughout the last 2 periods analyzed, namely from 108 per 100,000 py in 2011 to 2014 to 177 per 100,000 py in 2015 to 2017. In the non-MSM population, the IR of anal SCC doubled from 32 to 65 cases per 100,000 py when the periods from 2004 to 2010 and 2011 to 2017 were compared.

There were no cases of anal SCC among the women, which is surprising, because HIV-infected women show higher IRs than the general female population.[9] However, there were few women in the sample, which may explain the absence of SCC cases.

TABLE 5. Incidence rates and incidence ratios of anal SCC during the SCAN evaluation period (2011–2017) comparing SCAN with the overall $F/U_{2011–2017}$ study population and the subgroup of MSM

Study group	2011–2014				2015–2017				2011–2017			
	py	IR (CI)	IRR (CI)	p value	py	IR (CI)	IRR (CI)	p value	py	IR (CI)	IRR (CI)	p value
Overall												
SCAN	2091	100 (28.3–277)	1.07 (0.22–5.15)	0.350	2090	95.7 (26.9–264)	0.93 (0.18–4.80)	0.178	4181	95.7 (39.6–202)	0.87 (0.69–1.11)	0.269
$F/U_{2011–2017}$	7091	93 (48.7–167)			5080	98 (44.8–192.8)			12171	98.6 (60–154.7)		
MSM												
SCAN	2091	100 (28.3–277)	0.63 (0.45–0.88)	0.007	2090	95.7 (26.9–264)	0.55 (0.39–0.76)	<0.001	4181	95.7 (39.6–202)	0.41 (0.38–0.45)	<0.001
$F/U_{2011–2017}$	1650	181 (65.3–425)			1242	241 (86–565)			2892	201 (101–386)		

F/U = follow-up; IR = incidence rate; IRR = incidence rate ratio; MSM = men who have sex with men; Py = person-years; SCAN = screening and treating anal neoplasia.

More recent reports including periods up to 2012[20] reported that the IR of anal cancer increased over time, in general, and to over 70 per 100,000 py in MSM. Data from a prospective cohort where the IR was 107 per 100,000 py in a heterogeneous population, most the cases being MSM,[21] confirm our findings. These observations support keeping a close look on anal SCC in PLWH, with a special focus on MSM, until final data from the ANCHOR (https://anchorstudy.org/) and SPANC[22] studies are available.

Screening for anal SCC in people at risk has become an growing issue in recent years. In this context, the protective effect of a screening program to prevent anal cancer has been recently reported.[21] By contrast, a study conducted in the United States analyzing the incidence of anal cancer from 1998 to 2012 found a notable increase in the IR of anal cancer after implementation of HRA, the current standard to detect lesions of the anal canal.[23] Although the IR did not differ significantly between those who were enrolled in SCAN and those who were not, when all PLWH and the whole study period was considered, a significant aIRR of 0.3 was observed for MSM seen during the period SCAN was active. Although the IR of anal SCC appeared to have plateaued from 2011 through 2017 in both the SCAN and the $F/U_{2011–2017}$ subgroup, there was a significant increase over time in MSM not participating in the SCAN program in contrast to those who did. Moreover, all cases diagnosed in the SCAN group presented with T1/T2, without spread to nearby lymph nodes or distant sites, whereas, in the F/U group, only 25% showed T1/T2 at diagnosis, with 13 PLWH showing spread to lymph nodes and 2 even to distant sites. It is possible that screening for and subsequent treatment of HSIL have reduced the progression to invasive anal SCC in MSM. Furthermore, early diagnosis and treatment offers less aggressive but curative treatment options, reducing comorbidities and hence increasing quality of life and survival.

The fact that 50% of the PWLH diagnosed with anal SCC in SCAN were not compliant to the program because they missed scheduled screenings is concerning and, in accordance with expert opinions, highlighting the importance of adherence in screening programs.[24] This issue underlines the need to motivate people at risk of anal SCC to undergo screening and to improve screening uptake, similarly proposed by Vanhaesebrouck and colleagues in 2020.[25] Parameters such as age, tobacco consumption, and the level of education, factors associated with anal SCC in the present study, may be considered when working with individuals to rationalize screening visits.

Similar to the data from the US Veterans Affairs Immunologic Case Registry,[26] the IR for anal SCC among those who presented detectable HIV-RNA for longer than 25% of the follow-up period was numerically higher, although statistical significance was not reached. However, the immune reconstitution, reflected in CD4 T-cell count at study inclusion or its nadir, has been demonstrated to have an impact on the incidence of anal SCC in several studies.[23,26–29] Here, ImR was identified to protect individuals from the development of SCC in the overall population. This was also confirmed in the subpopulation of MSM, where patients with a baseline $CD4^+$ T-cell count below 350 cells/μL and no ImR during the follow-up showed an adjusted IRR of 1.8 versus the group of patients with a baseline cell count greater than 600 cells/μL. It is important to note that as much as 50% of anal SCCs were observed in this subpopulation. In this group, the effect appears to be strongest, but the IRRs were also significantly lower when ImR was achieved or, in those who presented with a baseline $CD4^+$ T-cell count of 350 to 600 cells/μL, was not achieved. In addition to ImR, PLWH who presented with CDC category C at baseline were more likely to develop anal SCC, with an IRR of 5 in all PLWH up to 11 in MSM, compared with those who presented with category A or B. It is therefore reasonable to speculate that, besides the main benefits, the ambitious aim of the Joint United Nations Programme on HIV/AIDS to achieve suppression of HIV in the majority of PLWH and the corresponding ImR will also reduce the risk of anal SCC[30] and further supports the implementation of HAART in clinical practice.

The main limitation of this study is the lack of complete adherence data. As mentioned earlier, a concerning 50% of the anal SCC patients in SCAN were not compliant to the program, and it is possible that the development of SCC could have been prevented otherwise. Because studies on this issue are warranted, adherence should be well documented. Until data are available, patients should be motivated to not only join a program, but also to be aware that adherence is likely to be crucial for the program to be successful. Another limitation is that, according to the protocol, only MSM were included in the SCAN group. Although the IR of anal SCC in MSM PLWH has been reported to be approximately twice as high as other male PLWH[9] and was 50% higher in this population, it has been found up to 70-fold higher than HIV-infected MSM. This is likely to be an important issue, and the benefit of screening non-MSM PWLH who present further risk factors for anal SCC should be evaluated.

One strength of this study is the sample size, because almost 4000 PLWH were included, which is, to our knowledge, the highest number analyzed in Spain. Furthermore, all patients were seen in the same clinic by the same medical team, which allows a comparison between the groups.

CONCLUSION

The IR of anal SCC in PLWH increased significantly throughout the study periods from 2004 to 2017, both in the overall population, and in the MSM subpopulation, who are at a higher risk to develop SCC per se, which was confirmed in this study. Immune reconstitution and

the clinical stage of HIV infection showed the strongest impact on anal SCC. Participation in the SCAN program significantly reduced the incidence of anal SCC in MSM, in whom focus should be placed, especially in those presenting CDC category C and advanced immune suppression.

REFERENCES

1. American Cancer Society. Cancer facts and figures 2017. Accessed January 9. 2021. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2017.html.
2. Islami F, Ferlay J, Lortet-Tieulent J, Bray F, Jemal A. International trends in anal cancer incidence rates. *Int J Epidemiol.* 2017;46:924–938.
3. American Cancer Society. Anal cancer. 2016. Accessed January 9, 2021. http://www.medicalnewstoday.com/articles/156549.php.
4. IARC. Agents classified by the IARC monographs. IARC Monographs. 2012. Accessed January 9, 2021. http://monographs.iarc.fr/ENG/Classification/List_of_Classifications.pdf.
5. Palefsky JM, Rubin M. The epidemiology of anal human papillomavirus and related neoplasia. *Obstet Gynecol Clin North Am.* 2009;36:187–200.
6. de Martel C, Shiels MS, Franceschi S, et al. Cancers attributable to infections among adults with HIV in the United States. *AIDS.* 2015;29:2173–2181.
7. Clifford GM, Polesel J, Rickenbach M, et al; Swiss HIV Cohort. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst.* 2005;97:425–432.
8. Daling JR, Madeleine MM, Johnson LG, et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. *Cancer.* 2004;101:270–280.
9. Piketty C, Selinger-Leneman H, Bouvier AM, et al. Incidence of HIV-related anal cancer remains increased despite long-term combined antiretroviral treatment: results from the french hospital database on HIV. *J Clin Oncol.* 2012;30:4360–4366.
10. Silverberg MJ, Lau B, Justice AC, et al; North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. *Clin Infect Dis.* 2012;54:1026–1034.
11. D'Souza G, Wiley DJ, Li X, et al. Incidence and epidemiology of anal cancer in the multicenter AIDS cohort study. *J Acquir Immune Defic Syndr.* 2008;48:491–499.
12. Franceschi S, Lise M, Clifford GM, et al; Swiss HIV Cohort Study. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. *Br J Cancer.* 2010;103:416–422.
13. Viciana P, Milanés-Guisado Y, Fontillón M, et al. High-risk human papilloma virus testing improves diagnostic performance to predict moderate- to high-grade anal intraepithelial neoplasia in human immunodeficiency virus-infected men who have sex with men in low-to-absent cytological abnormalities. *Clin Infect Dis.* 2019;69:2185–2192.
14. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep.* 1992;41:1–19.
15. Silverberg MJ, Lau B, Achenbach CJ, et al; North American AIDS Cohort Collaboration on Research and Design of the International Epidemiologic Databases to Evaluate AIDS. Cumulative incidence of cancer among persons with hiv in North America: a cohort study. *Ann Intern Med.* 2015;163:507–518.
16. Johnson LG, Madeleine MM, Newcomer LM, Schwartz SM, Daling JR. Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973-2000. *Cancer.* 2004;101:281–288.
17. Diamond C, Taylor TH, Aboumrad T, Bringman D, Anton-Culver H. Increased incidence of squamous cell anal cancer among men with AIDS in the era of highly active antiretroviral therapy. *Sex Transm Dis.* 2005;32:314–320.
18. Colón-López V, Shiels MS, Machin M, et al. Anal cancer risk among people with HIV infection in the United States. *J Clin Oncol.* 2018;36:68–75.
19. Hernández-Ramírez RU, Shiels MS, Dubrow R, Engels EA. Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study. *Lancet HIV.* 2017;4:e495–e504.
20. Jin F, Vajdic CM, Law M, et al. Incidence and time trends of anal cancer among people living with HIV in Australia. *AIDS.* 2019;33:1361–1368.
21. Revollo B, Videla S, Llibre JM, et al. Routine screening of anal cytology in persons with human immunodeficiency virus and the impact on invasive anal cancer: a prospective cohort study. *Clin Infect Dis.* 2020;71:390–399.
22. Machalek DA, Grulich AE, Hillman RJ, et al; SPANC Study Team. The Study of the Prevention of Anal Cancer (SPANC): design and methods of a three-year prospective cohort study. *BMC Public Health.* 2013;13:946.
23. Barnell GM, Merchant M, Lam JO, Silverberg MJ. Early outcomes of a high-resolution anoscopy-based anal cancer screening program among people with HIV enrolled in an integrated health care system. *J Acquir Immune Defic Syndr.* 2019;81:292–299.
24. Goldstone SE. Anal cancer prevention: Solving the puzzle piece by piece. *Cancer.* 2020;126:1376–1378.
25. Vanhaesebrouck A, Pernot S, Pavie J, et al. Factors associated with anal cancer screening uptake in men who have sex with men living with HIV: a cross-sectional study. *Eur J Cancer Prev.* 2020;29:1–6.
26. Chiao EY, Hartman CM, El-Serag HB, Giordano TP. The impact of HIV viral control on the incidence of HIV-associated anal cancer. *J Acquir Immune Defic Syndr.* 2013;63:631–638.
27. Aldersley J, Lorenz DR, Misra V, Uno H, Gabuzda D. Increased risk of anal squamous cell carcinoma in HIV-positive men with prior hepatitis B virus infection. *AIDS.* 2019;33:145–152.
28. Hernández-Ramírez RU, Qin L, Lin H, et al; North American AIDS Cohort Collaboration on Research and Design of the International Epidemiologic Databases to Evaluate AIDS. Association of immunosuppression and human immunodeficiency virus (HIV) viremia with anal cancer risk in persons living with HIV in the United States and Canada. *Clin Infect Dis.* 2020;70:1176–1185.
29. Schwartz LM, Castle PE, Follansbee S, et al. Risk factors for anal HPV infection and anal precancer in HIV-infected men who have sex with men. *J Infect Dis.* 2013;208:1768–1775.
30. UNAIDS. 90-90-90: An ambitious treatment target to help end the AIDS epidemic. 2020. Accessed January 9, 2021. https://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf.