Circumcision and penile human papillomavirus prevalence in human immunodeficiency virus-infected men: heterosexual and men who have sex with men

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Abstract

Male circumcision is associated with a lower risk of penile human papillomavirus (HPV) infection in human immunodeficiency virus (HIV) uninfected men. Few studies have evaluated the role of male circumcision in penile HPV infection in HIV-infected men. The aim of this cross-sectional study was to examine the association between male circumcision and the prevalence of penile HPV infection among HIV-infected men—both men who have sex with men (MSM) and heterosexual men. Samples from 706 consecutive men included in the CARH-MEN cohort (overall 24% circumcised: 26% of MSM, 18% of heterosexual men) were examined by Multiplex-PCR. In the overall group (all HIV-infected men included), the prevalence of any penile HPV infection was 22% in circumcised men and 27% in uncircumcised men (OR = 1.0, 95% CI 0.6–1.6, adjusted analysis). In the circumcised group the overall prevalence of HPV infection was 22% in MSM and 24% in the heterosexual men, whereas in the uncircumcised group the prevalence was 26% and 28%, respectively. The prevalence of high-risk HPV types tended to be lower in the circumcised MSM (14% vs 21%, OR = 0.6, 95% CI 0.3–1.1, p 0.088), but it was similar in the heterosexual men (18% in circumcised vs 20% in uncircumcised). These results suggest that male circumcision may be associated with a lower prevalence of oncogenic high-risk penile HPV infection in HIV-infected MSM.

Keywords: Human papillomavirus, male circumcision, men who have sex with men, heterosexual HIV-infected men
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Introduction

There is evidence that circumcision reduces the risk of human immunodeficiency virus (HIV) acquisition in heterosexual men by about 60% and it is recommended as one of the HIV prevention strategies [1,2]. Though the prevalence of penile human papillomavirus (HPV) infection varies around the world [3], male circumcision is associated with a reduced risk of penile HPV infection [4,5].

Infection with high-risk (HR) oncogenic HPV types is the aetiological cause of several specific squamous cancers, such as cervical, anal and oropharyngeal cancers. In contrast, infection with low-risk (LR) HPV types (6 and 11) is the aetiological cause of genital warts [6,7].

Most studies focusing on the role of circumcision in penile HPV infection have been performed on HIV-uninfected men. Only one randomized clinical trial of male circumcision among HIV-infected men has been conducted reporting a protective effect of circumcision on the prevalence of HR-HPV types 24 months after the procedure [8]. However, no information is available about the role of circumcision in HIV-infected men who have sex with men (MSM). The objective of this cross-sectional analysis was to provide evidence about the association between male circumcision and the

prevalence of penile HPV infection among HIV-infected men (MSM and heterosexual) in Spain.

Patients and Methods

Study design

A cross-sectional analysis, based on the first (baseline) visit to the CARH-MEN (Can Ruti HIV-positive Men) cohort, was performed. This cohort was a prospective, single-centre study including HIV-positive outpatient men who were annually assessed for HPV infection of anus, penis and mouth. The protocol, amendments and other materials were approved by the hospital's independent ethics committee [9]. Consecutive patients, who attended their AIDS routine control, were informed about the study and written informed consent was obtained for recruitment to the current study.

HIV-positive men ≥18 years old, without history of (or current) HPV-related pathology in anus, penis or mouth were included in the CARH-MEN cohort between January 2005 and May 2009. At the baseline visit, all participants completed a detailed self-administered baseline questionnaire, and a clinical examination (visual inspection) of the three body areas studied (anal canal, penis and mouth) and a digital rectal examination were performed. Samples from the three areas were collected for detecting HPV infection. All patients were monitored annually. At each annual visit, questionnaire and clinical examination were performed. The following data were collected: date of birth, date of HIV-positive diagnosis, baseline CD4 cell counts (the closest value determined during participants' usual clinical follow-up visits in HIV Unit before the cytological sample collection), CD4 nadir counts (the lowest CD4 value of each patient abstracted from medical records), plasma HIV viral load (the closest value determined before the sample collection), highly active antiretroviral therapy previous to inclusion and time on highly active antiretroviral therapy, history of sexually transmitted infections, alcohol use and smoking history, sexual behaviour and number of sexual partners. CD4 cell count and CD4 nadir were determined by flow cytometry; HIV viral load was measured by Nuclisens (bioMérieux, Inc., Durham, NC, USA).

Penile sample collection

Trained clinicians collected the first 2 cm of the urethral epithelium with a dacron urethral swab. A second saline prewetted dacron swab was used to obtain cells from the four quadrants of the penile shaft, glans and coronal sulcus. The glans was first scratched with sand paper to increase the cellular yield. Both penile samples were pooled in the same tube and suspended in 1 mL of 0.1 M phosphate-buffered saline and the solution was stored at −20°C until analysis.

HPV testing and genotyping

DNA extraction was performed by the Qiamp Viral DNA kit (QIAGEN, Hilden, Germany). HPV detection and typing were performed using the commercial Multiplex Fluorescent-PCR Kit (F-HPV typing™, Molgentix SL, Barcelona, Spain) in accordance with the manufacturer's instructions. The assay permits the detection of 13 HR-HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68; and two LR-HPV types: 6, 11. A human short tandem repeat sequence included in the same multiplex was amplified as an internal control to check for DNA integrity and the absence of PCR inhibitors. Products were analysed by capillary electrophoresis on an ABI 3130 XL genetic analyser and GeneMapper 4.0 software (Applied Biosystems, Foster City, CA, USA). Each PCR run included HPV-positive and HPV-negative controls. Particular care was taken to prevent carry-over contamination by separating pre-PCR and post-PCR areas in all PCR experiments.

Definitions

Sexual status, i.e. MSM or heterosexual, was obtained through the questionnaire, and then verified by checking the medical record. Circumcision status was obtained through the questionnaire, and during the visual clinical inspection at baseline visit. Existence of a current HPV infection was considered when one or more HPV types were detected in a sample, single or multiple HPV infections if one or more HPV types were detected respectively. LR-HPV infection was defined as when only HPV-6 and/or HPV-11 was detected, and HR-HPV infection as when any of HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 or 68 was detected. No HPV infection was defined as non-detectable HPV types.

Statistical analysis

Three populations were analysed: the entire group (all HIV-infected men included in the study), the MSM group and the heterosexual group. Baseline characteristics were summarized with standard descriptive statistics and a descriptive analysis was carried out. Differences between circumcised and uncircumcised men were evaluated by the chi-square test for qualitative variables. Differences in the prevalence of type-specific infections were also assessed by the circumcision status. Odds ratios (OR) for prevalence were estimated as well as the corresponding 95% CI. The association between potential explanatory variables and HPV infection was tested. A bivariate regression model was performed to obtain an indication of the relevance of the explanatory variables for the risk of HPV infection. A multivariate regression

model using a stepwise selection of variables was adjusted to the following covariates: the presence of circumcision; history of anal warts; history of sexually transmitted infections; receptive anal intercourse (yes/no); number of lifetime sexual partners (>25); HIV infection time (years); plasma HIV-1 RNA (undetectable <50 copies/mL); nadir CD4 counts (<200 cells/mm^3); and CD4 counts at baseline (<200 cells/mm^3). A p value ≤0.05 was considered statistically significant. Data analysis was carried out using SPSS version 15.0 statistical software (Chicago, IL, USA).

Results

Patients' characteristics

The CARH-MEN cohort included 733 HIV-positive men (538 MSM and 195 heterosexuals), a total of 706 (96%) patients with available and concordant circumcision information from clinician assessment and patients' self-reported questionnaire were included in the present analyses. The overall prevalence of circumcision was 24% (167/706): 26% (133/516) in MSM and 18% (34/190) in heterosexual men (OR = 1.6; 95% CI 1.0–2.4, p 0.029). There were no significant differences in the baseline characteristics between circumcised and uncircumcised patients, except for a slightly higher proportion of MSM in the circumcised group (Table 1).

Sixty-nine (10%) penile samples were not suitable for HPV detection because of the lack of amplification of the internal PCR control. Therefore, penile HPV prevalence was estimated on 637 HIV-infected men: 143 circumcised (110 MSM and 33 heterosexual) and 494 uncircumcised (340 MSM and 154 heterosexual).

Overall HIV-infected men group

The overall prevalence of any penile HPV infection was 26% (163/637, 95% CI 22–29), 22% (32/143, 95% CI 16–30) in the circumcised group and 27% (131/494, 95% CI 23–31) in the uncircumcised group. This difference was not statistically significant (Table 2).

The risk factors associated with any penile HPV infection in the adjusted analysis were a history of anal warts (OR = 2.4, 95% CI 1.5–3.8), receptive anal intercourse (OR = 3.3, 95% CI 2.1–5.4), number of sexual lifetime partners (>25) (OR = 2.1, 95% CI 1.2–3.7) and CD4 counts lower than 200 cells/mm^3 (OR = 1.4, 95% CI 1.1–2.0). In contrast, undetectable HIV load in plasma (OR = 0.6, 95% CI 0.3–0.9) was a protective factor for any HPV infection.

The analysis of any penile HPV infection prevalence by circumcision status and stratified by plasma HIV load (detectable: >50 copies/mL and undetectable: <50 copies/mL), and by CD4 nadir counts (200 cells/mm^3) did not show differences.

HPV-16 (6% (8/143) circumcised, 5% (26/494) uncircumcised) was the most common type detected among the high-risk types, and HPV-6 (7% (10/143) circumcised, 9% (44/494) uncircumcised) was commonest among the low-risk types (Fig. 1). The only statistical difference observed in the analyses for specific types was for HPV-51, which was less prevalent in circumcised men (1% vs 4%, OR = 0.2, 95% CI 0.1–0.9, p 0.048).

TABLE 1. Baseline characteristics of human immunodeficiency virus (HIV) -infected men based on circumcision status

Baseline characteristics	Circumcised *n* = 167	Uncircumcised *n* = 539	p-value
Age			
Median years (Range)	40 (21–70)	42 (20–77)	0.256
20–29 years, *n* (%)	11 (6.6)	42 (7.8)	
30–39 years, *n* (%)	65 (38.9)	171 (31.7)	
40–49 years, *n* (%)	67 (40.1)	233 (43.2)	
50–59 years, *n* (%)	17 (10.2)	72 (13.4)	
60–69 years, *n* (%)	6 (3.6)	17 (3.2)	
>69 years, *n* (%)	1 (0.6)	4 (0.7)	
Time of known HIV (years)			
Median (Range[a])	9 (0–24)	9 (0–26)	0.582
AIDS diagnosis (Yes), *n* (%)	28 (16.8)	84 (15.6)	0.715
HIV plasma load < 50 HIV RNA copies/mL, *n* (%)	111 (66.9)	356 (66.8)	0.986
CD4 cell count at baseline, *n* (%)			
<200 cells/mm^3	11 (6.6)	33 (6.2)	0.979
200–500 cells/mm^3	70 (42.2)	225 (42.2)	
>500 cells/mm^3	85 (51.2)	275 (51.6)	
CD4 nadir Mean (95% CI)	255 (227–282)	260 (245–276)	0.876
<200 cells/mm^3, *n* (%)	67 (40.1)	213 (39.5)	0.889
HAART previous to inclusion (Yes)			
Number (%)	136 (81.4)	453 (84)	0.428
Duration of HAART (years)			
Median (25–75 centile)	6 (5–6.7)	6 (5.6–6)	0.887
History of STI (Yes)			
Number (%)	63 (37.7)	235 (43.6)	0.176
Alcohol history, *n* (%)			
Never	39 (24.7)	135 (25.8)	0.357
Current	93 (58.9)	278 (53.2)	
Past	26 (16.5)	110 (21)	
Smoking history, *n* (%)			
Never	32 (20.3)	126 (24.1)	0.129
Current	98 (62)	277 (53)	
Past	28 (17.7)	120 (22.9)	
Injected drug user, *n* (%)			
Never	135 (84.9)	416 (79.8)	0.329
Current	2 (1.3)	6 (1.2)	
Past	22 (13.8)	99 (19)	
Number of sexual partners, *n* (%)			
1 partner	1 (0.6)	7 (1.3)	0.906
2–9 partners	21 (12.6)	78 (14.5)	
10–25 partners	17 (10.2)	56 (10.4)	
>25 partners	104 (62.3)	322 (59.7)	
Men having sex with men, *n* (%)	133 (79.6)	383 (71.1)	0.029
History of RAI (Yes), *n* (%)	98 (67.1)	293 (60.4)	0.143

HAART, highly active antiretroviral therapy; STI, sexually transmitted infection; RAI, receptive anal intercourse.
[a]Range (maximum–minimum values).

TABLE 2. Prevalence of human papillomavirus (HPV) infection in human immunodeficiency virus (HIV) -infected men according to circumcision status and sexual behaviour

	Overall HIV-infected men (*n* = 637)					HIV-infected MSM (*n* = 450)					HIV-infected heterosexuals (*n* = 187)				
	Circumcised *n* = 143		Uncircumcised *n* = 494		Crude values	Circumcised *n* = 110		Uncircumcised *n* = 340		Crude values	Circumcised *n* = 33		Uncircumcised *n* = 154		Crude values
Penile HPV infection	*n*	% (95% CI)	*n*	% (95% CI)	OR (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	OR (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	OR (95% CI)
Any type	32	22 (16–30)	131	27 (23–31)	0.8 (0.5–1.2)	24	22 (14–30)	88	26 (21–30)	0.8 (0.5–1.3)	8	24 (11–42)	43	28 (21–36)	0.8 (0.4–2.0)
High-risk types[a]	21	15 (9–22)	101	20 (17–24)	0.6 (0.4–1.1)	15	14 (8–21)	70	21 (16–25)	0.6 (0.3–1.1)	6	18 (7–35)	31	20 (14–27)	0.9 (0.3–2.3)
Low-risk types[b]	11	8 (4–14)	30	6 (8–14)	0.7 (0.4–1.4)	9	8 (4–17)	18	5 (4–10)	1.5 (0.6–3.4)	2	6 (1–24)	12	8 (5–16)	0.7 (0.2–3.5)
Single (1 type)	25	17 (12–25)	86	17 (14–21)	1.0 (0.6–1.6)	19	17 (11–26)	55	16 (12–20)	1.1 (0.6–1.9)	6	18 (7–35)	31	20 (14–27)	0.8 (0.3–2.3)
Multiple (≥2 types)	7	5 (2–10)	45	9 (7–12)	0.5 (0.2–1.1)	5	4 (1–10)	33	10 (7–13)	0.4 (0.2–1.2)	2	6 (1–20)	12	8 (4–13)	0.7 (0.2–3.6)

MSM, men who have sex with men.
[a]Included infections with any of the high-risk types:HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68.
[b]Included infections only containing low-risk types: HPV-11 and/or HPV-6.

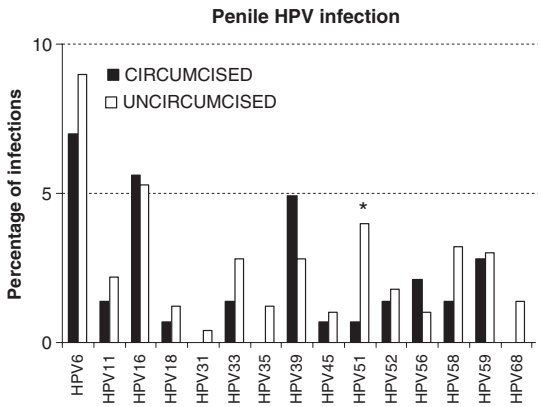

FIG. 1 Prevalence of infection with human papillomavirus (HPV) type: low-risk (HPV-6, -11) and high-risk oncogenic (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -68) by circumcision status.

High-risk HPV types were detected in all multiple penile HPV infections. History of anal warts and nadir CD4 counts below 200 cells/mm^3 were associated with higher rate of infection with HR-HPV (Table 3).

TABLE 3. Predictive factors associated with the presence of high risk human papillomavirus (HPV) types in penis of human immunodeficiency virus (HIV) -infected men in the three populations analysed: overall group (all HIV-infected patients included in the study), men who have sex with men group and heterosexual men; multivariate analyses

High risk HPV infection	Adjusted[a] OR (95% CI)	p-value[b]
Overall (*n* = 637)		
Circumcision (yes/no)	0.7 (0.4–1.2)	0.158
History of anal warts[c]	1.7 (1.1–2.6)	0.023
Nadir CD4 counts (<200 cells/mm^3)	1.6 (1.1–2.5)	0.026
Men who have sex with men (*n* = 450)		
Circumcision (yes/no)	0.6 (0.3–1.1)	0.088
Nadir CD4 counts (<200 cells/mm^3)	1.7 (0.9–3.0)	0.079
CD4 counts at baseline (<200 cell/mm^3)	2.6 (0.9–7.7)	0.086
Heterosexual men (*n* = 187)		
Circumcision (yes/no)	0.9 (0.3–2.6)	0.784
Undetectable plasma HIV-1 RNA (<50 copies/mL)	0.4 (0.2–0.8)	0.014

[a]Multivariate analysis was adjusted for circumcision and the following covariates: history of anal warts, history of sexual transmitted infections, receptive anal intercourse (yes/no), number of lifetime sexual partners (>25), HIV infection time (years), plasma HIV-1 RNA (non-detectable <50 copies/mL), nadir CD4 counts (<200 cells/mm^3), and CD4 counts at baseline (<200 cells/mm^3).
[b]p <0.05, differences statistically significant.
[c]Included men with history or presence of anal condylomatous lesions at baseline.

MSM HIV-infected group

The prevalence of any penile HPV infection in MSM was 25% (112/450, 95% CI 21–29) (Table 2). The only risk factor associated with any penile HPV infection in the adjusted analysis was a history of anal warts (OR = 2.7, 95% CI 1.4–5.2). CD4 counts >200 cells/mm^3 were shown to be a protective factor (OR = 0.5, 95% CI 0.3–0.8).

The prevalence for HR-HPV types tended to be lower in circumcised MSM compared with uncircumcised MSM (14% vs 21%, OR = 0.6, 95% CI 0.3–1.1) (Table 2). Circumcision was associated with a statistically non-significant lower frequency of penile HR-HPV infection (OR = 0.6, 95% CI 0.3–1.1, p 0.088, adjusted analysis) (Table 3).

Heterosexual HIV-infected group

The prevalence for any penile HPV infection in heterosexual men was 27% (51/187, 95% CI 21–34). No differences were observed between the circumcised and uncircumcised groups (Table 2). No significant risk factor in the adjusted analysis

was found, although having a history of anal warts showed similar results to the MSM group (OR = 1.9, 95% CI 0.9–4.0, p 0.065).

A similar prevalence of penile HR-HPV infection was observed by circumcision status (Table 2). An undetectable plasma level of HIV load was a protective factor for HR-HPV (Table 3).

Discussion

To our knowledge, this is the first study providing data on the prevalence of penile HPV infection by circumcision status in HIV-infected MSM and heterosexual men without a history of penile warts in a developed country (Spain). The prevalence of any penile HPV infection was 22% in the circumcised men and 27% in uncircumcised men. This prevalence was similar between MSM and heterosexual men, regardless of circumcision status. However, the prevalence of HR-HPV types tended to be lower in circumcised MSM.

A recent meta-analysis, based mainly on HIV-negative men, indicated that circumcised men were less likely to have prevalent genital HPV infection than uncircumcised men, but with important between-study heterogeneity [10]. Only one published randomized clinical trial studied the effect of male circumcision on penile HPV infection among HIV-infected men [8]. This randomized clinical trial, carried out in Africa, randomized HIV-infected patients to immediate versus delayed (at 24 months) circumcision, showing an effect of circumcision on prevalence of HR-HPV types at 24 months (OR = 0.49; 95% CI 0.26–0.93). This study also showed a high incidence of HPV (50% over 24 months), borderline evidence of a protective effect of circumcision on HPV incidence (RR = 0.68; 95% CI 0.44–1.04) and no evidence of a protective effect of circumcision on HPV clearance (RR = 1.09; 95% CI 0.94–1.27) [8]. It is noteworthy that the prevalence of penile HPV infection observed in our study in uncircumcised HIV-infected men was lower (27%) than the prevalence of the abovementioned randomized clinical trial at baseline. Furthermore, it should be taken into account that 73% of the HIV-infected men included in our study were MSM (22% prevalence of penile HPV infection). Moreover, in a previous study of the present cohort a high prevalence of anal condylomata was related to a high prevalence of HR-HPV and high-grade squamous intraepithelial lesions in the anal canal [11]. Hence, it is reasonable to think that the anus may be a reservoir for these types and might contribute to penile HPV infection or re-infections.

Some limitations need to be considered in the interpretation of these results. The study design (cross-sectional) cannot provide evidence on the effect of male circumcision on penile HPV infection; it only shows associations. Circumcision prevalence varies, depending on the country, from 6% (the Netherlands), 21% (UK) and 80% (USA and South Korea) to 87% (Kenya) [12]. The prevalence of circumcision found among the HIV-infected men (24%) was that expected for European countries. Different rates of circumcision may be responsible for the diversity of results between studies. The small sample size of circumcised heterosexual HIV-infected men does not allow for conclusions to be drawn for this subpopulation in our study. Other drawbacks may be the anatomical site of HPV sampling (glans/corona, penile shaft, scrotum, urethra). In our study, the penile sample was pooled from the urethral epithelium, penile shaft, glans and coronal sulcus. In consequence, it was not possible to provide information on HPV infection for each distinct area. The HPV-DNA detection method used only targets 13 HR-HPV and two LR-HPV types. The HR-HPV types are the most commonly associated with malignant lesions in anogenital sites and the LR-HPV types are the most involved in anogenital condylomatous lesions. Therefore, the method used for HPV-DNA detection provides information on clinically relevant types.

In summary, male circumcision may be associated with a lower prevalence of oncogenic high-risk penile HPV types in HIV-infected MSM. Further longitudinal clinical studies, preferably randomized clinical trials, are needed in different areas of the world, to assess the potential benefit of male circumcision on penile HPV infection in HIV-infected men, thereby preventing potential penile cancer.

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Transparency Declaration

None declared.

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