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Title page

Full title: **Association of oncogenic and non-oncogenic human papillomavirus with HIV incidence**

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Running head: The HPV-HIV association

Abstract/key word page**Association of oncogenic and non-oncogenic human papillomavirus with HIV incidence****Word count: 199 (max=200)**

Objective: Little is known about the interaction between HPV and HIV. This study aimed to explore the association of oncogenic (HR) and non oncogenic (LR) human papillomavirus (HPV) with HIV incidence.

Methods: We used urethral swabs collected at the last follow-up visit of a male circumcision trial conducted in Orange Farm (South Africa). Swabs analyses and HPV genotyping were performed by polymerase chain reaction. We estimated HIV adjusted incidence rate ratios (aIRR) and 95% confidence intervals (CI) using survival analysis. Background characteristics, male circumcision status, sexual behavior, HPV status and other sexually transmitted infections were used as covariates.

Results: The prevalence of HR and LR HPV was 14.0% (95%CI: 12.4 to 15.7) and 17.3% (95%CI: 15.6 to 19.2), respectively. When controlling for HR-HPV status, LR-HPV status was not associated with HIV incidence (aIRR = 1.13, 95%CI: 0.40 to 3.16; $P = 0.82$). When controlling for all covariates, HIV incidence increased significantly with HR-HPV positivity (aIRR=3.76, 95%CI: 1.83 to 7.73, $P < 0.001$) and with the number of HR-HPV genotypes (adjusted- P linear trend = 0.0074).

Conclusions: Several explanations could account for our findings. One is that HR-HPV facilitates HIV acquisition. The association of HPV with HIV acquisition requires further investigations.

Keywords : HIV; HPV; male circumcision; Africa; men

Word count: 2375

Genital human papillomavirus (HPV) genotypes are divided into "high-risk" (HR) and "low-risk" (LR) genotypes, on the basis of their oncogenic potential.¹ LR-HPVs are most commonly associated with non-malignant lesions such as genital warts,² while HR-HPV are found in virtually all pre-malignant or malignant lesions of the genitals and are associated with cancers of the cervix, vulva, vagina, anus, and penis.¹⁻⁵

Genital HPV, which is highly infectious, is thought to be vastly prevalent among men and women in sub-Saharan Africa, and cervical cancer, attributable to HR-HPV at over 99%,⁶ is the leading cause of cancer mortality among women in Southern Africa.¹ HIV infection is also correlated with invasive cervical cancer, since it is a recognized AIDS defining condition. In view of the importance of both infections in the burden of morbidity and mortality in the region, research on the epidemiologic and etiologic association of HIV and HPV is of great public health relevance.

Most studies investigating the association between genital HPV and HIV have focused on the effects of HIV infection on HPV prevalence, incidence and genotype distribution. Several studies found that HIV positive status was strongly associated with higher HPV prevalence in men and women,^{1,7-11} higher HR-HPV prevalence,^{7,9-13}, higher HPV incidence,¹⁴, higher prevalence of infections with multiple HPV genotypes⁷⁻¹², and higher frequency of HPV lesions in multiple locations.¹²

The objective of this study was to explore the association of HR- and LR-HPV with HIV incidence. For these analyses, we used longitudinal data collected in Orange Farm (South Africa), an area of high HIV prevalence,¹⁵ during a male circumcision randomized controlled trial which demonstrated a reducing effect of male circumcision on the acquisition of HIV.¹⁶

METHODS

Collection of data

The technical details of the trial (ANRS-1265) have been published elsewhere.¹⁶ Briefly, male participants, aged 18 to 24, were recruited from the general population of the township of Orange Farm (South Africa) and followed up for 21 months. During each follow-up visit at 3, 12 and 21 months, data on background information and sexual behavior was collected, and participants' circumcision status was assessed by a nurse.

As described in previous publications, blood samples collected at each follow-up visit were tested for HIV and Herpes Simplex Virus type 2 (HSV-2), and urine samples collected at the 21-month visit were tested for *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and *Trichomonas vaginalis*.¹⁶⁻¹⁸

To conduct HPV testing, a urethral cotton swab, introduced in the first 5 mm of the urethra, was collected by the same nurse from participants coming for the 21-month visit. For practical reasons, this collection took place from October 1st, 2005 to November 24th, 2006. The data used in the current study includes 596 additional follow-up visits which were collected after the database used to report the results of the trial on HIV incidence¹⁶ was completed. Furthermore, the database also includes data from the analyses of 490 additional urethral swabs which were collected from October 1st, 2005 to March 6th, 2005 but were not used in the report on HR-HPV prevalence among trial participants,¹⁹ because they had been mislaid by the testing laboratory.

Laboratory methods

Swabs specimens for HPV testing were frozen at -20°C immediately after collection and kept frozen until processing. DNA was extracted from urethral swabs using the MagNA Pure LC instrument, with the Roche MagNA Pure LC DNA I Isolation Kit (Roche Diagnostics, Mannheim, Germany). Swabs were lysed in 500 µl of the kit lysis buffer for 30 minutes at room temperature. The MagNa Pure external lysis protocol was used to extract DNA from the lysis buffer into a 100-µl eluate. 50 µl of the eluate was used for screening (Roche Amplicor HPV test, Roche Diagnostics, Branchburg, NJ, USA) and 50-µl eluate was used for genotyping (Roche Linear Array Genotyping test, Roche Diagnostics, Branchburg, NJ, USA). 14/1771 (0.85%) samples with a negative internal beta-globin PCR control were excluded. All positive results were genotyped. This standardized PCR-based method can detect 13 HR-HPV genotypes (i.e., genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) and 24 LR-HPV genotypes (i.e., genotypes 6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 66, 67, 69, 70, 71, 72, 73, 81, 82, 83, 84, IS39 and CP6108). Because of the combined probe of the assay for HPV-52 and in order to be conservative, samples were classified as HPV-52 positive only when they were negative for genotypes 33, 35 and 58. A HR-HPV sample was defined as positive if at least one HR-HPV was detected, likewise for LR-HPV. Samples could be positive for both HR-HPV and LR-HPV. In some analyses, we considered multiple HR-HPV samples, defined as samples where at least two HR-HPV genotypes were detected.

Data analysis

The main analyses were performed on a subset of 1683 participants who were HIV-negative at inclusion and were tested for both HPV and HIV at the 21-month visit. They represent 1683/2949 (57.1%) of the participants who were tested for HIV at the 21-month visits. The associations of HR-HPV and LR-HPV statuses with age were tested using logistic regression, controlling for ethnic group, education, circumcision status and condom use. HIV incidence rate and HIV incidence rate ratios (IRRs) were estimated among participants by a piecewise exponential proportional hazards model implemented using univariate log-Poisson regression.²⁰⁻²² The effect of LR-HPV status on HIV incidence was tested after controlling for HR-HPV status. The multivariate effect of HR-HPV status on HIV incidence was estimated controlling for the following covariates: ethnic group, age, education, number of lifetime partners, condom use in the past 12 months, circumcision status, HSV-2 status at inclusion, HSV-2 acquisition during follow-up, and the status at the 21-month visit for the following sexually transmitted diseases: *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and *Trichomonas vaginalis*.

To estimate the mean duration between HIV acquisition and swab collection for HPV testing, the date of HIV acquisition was estimated for each participant as the date at mid point between the last follow-up visit with an HIV-negative test result and the first follow-up visit when HIV infection was detected.

The confidence intervals of the percentages were calculated using Bayesian estimation.²³ Statistical analyses were performed using the statistical package SPSS for Windows version 8 (SPSS, Chicago, Illinois, United States) and R version 2.6.2.²⁴

In two ancillary intention-to-treat analyses, we assessed whether the additional data on HIV and HPV had any impact, first on the estimated effect of MC on HIV incidence and secondly on the estimated effect of MC on HPV prevalence. These effects were recalculated using the methods described in the corresponding publications.^{16,19}

Ethics

The research protocol was reviewed and approved by the University of Witwatersrand Human Research Ethics Committee (Medical) on February 22nd, 2002 (protocol study no. M020104). The trial was also approved by the Scientific Commission of the French National Agency for AIDS Research (ANRS; protocol study no. 1265; 2002, decision No. 50) and authorization was obtained from the City of Johannesburg, Region 11, on 25 February 2002.

This trial has been registered at <http://www.clinicaltrials.gov> under the number NCT00122525.

RESULTS

Population characteristics

The background characteristics of the 1683 participants included in this study are presented in Table 1. The proportion of participants infected with HPV increased with age (P -linear trend=0.0024). The prevalence of HR-HPV was significantly higher than the prevalence of LR-HPV ($P < 0.001$, McNemar test). The number of HR-HPV genotypes and LR-HPV genotypes among those infected with at least one HPV genotype were correlated ($P < 0.001$, Spearman's rank correlation test). The prevalences of LR-HPV and HR-HPV were also correlated ($P < 0.001$, Fisher's Exact Test). Among the participants infected with a HR-HPV, 70.5% (95%CI: 65.2 to 75.6) were also infected with a LR-HPV, and among all those infected with a LR-HPV, 87.3% (95%CI: 82.7 to 91.1) were also infected with a HR-HPV. The distributions of HR- and LR-HPV genotypes are listed in Table 2. As shown in this table, the two most frequent HR-HPV were genotypes 16 and 18 and HPV 6 was by far the most frequent LR-HPV. After controlling for age, ethnic group, education, circumcision status, sexually transmitted infections and condom use, HR-HPV and LR-HPV statuses were significantly associated with number of lifetime partners with P -values for linear trend of 0.025 and 0.022, respectively.

HIV prevalence and incidence

During follow-up, 33/1683 (2.0%) participants became HIV-positive. At the 21-month follow-up visit, HIV prevalence among those HR-HPV negative was 1.1% (15/1391) and 6.2% (18/292) among those HR-HPV positive (RR=5.72 (2.88-11.3) $P < 0.001$).

HIV incidence was higher among those with at least one HPV genotype compared to those with no detected HPV in univariate analysis: 5.26 /100 person-year (py) versus 0.96 /100py; (IRR = 5.45, 95%CI: 2.72 to 10.9; $P < 0.001$) and when controlling for covariates (aIRR = 4.55, 95%CI: 2.23 to 9.28; $P < 0.001$).

When controlling for HR-HPV status, LR-HPV status was not associated with HIV incidence (aIRR = 1.13, 95%CI: 0.40 to 3.16; $P = 0.82$) Table 3 indicates the effect of HR-HPV status and covariates on HIV incidence. In the univariate and multivariate analyses, HIV incidence was significantly higher among HR-HPV positive participants. HIV incidence

increased with the number of HR-HPV genotypes involved in multiple infections in univariate analysis (figures 1 & 2). In multivariate analysis, among those positive for at least one HR-HPV genotype, HIV incidence increased on average by a factor of 1.55 (95%CI: 1.12 to 2.14; $P = 0.0074$) when the number of HR-HPV genotypes increased by one unit.

The mean duration between the estimated date of HIV acquisition and the date of the swabbing for the detection of HPV was 10.2 months (interquartile range; 4.6 to 13.6 months).

Effect of MC on HIV incidence and on HR-HPV prevalence

With the additional follow-up visits and HIV results, there were 21 HIV infections (incidence rate 0.82 per 100 person-years) in the intervention group and 52 (2.1 per 100 person-years) in the control group, corresponding to an HIV incidence rate ratio of 0.40 (95%CI: 0.24% to 0.66%; $P < 0.001$). The prevalences of HR-HPV among the intervention and control groups were 14.5% (129/890) and 22.1% (191/863), respectively, with a prevalence ratio of 0.65 (0.52 to 0.82) ($P < 0.001$). Almost identical estimates were reported in the initial publications: 0.40 for HIV risk ratio and 0.66 for the HPV prevalence rate ratio.^{16,19}

DISCUSSION

Using longitudinal data from a male circumcision trial, this study revealed for the first time a significant association of oncogenic HPV with HIV incidence among African young men. Conversely, this study did not demonstrate an association of non oncogenic HPV with HIV incidence.

This study has four limitations. Firstly, as with any observational study, no causal relationship between HPV and HIV can be concluded from the findings. Secondly, urethral sampling has been shown to be unaffected by circumcision status,^{19,25} which is important when studying samples with circumcised and uncircumcised men as it is the case in this study. However, it has the disadvantage of underestimating the presence of genital HPV.^{26,27} This underestimation is not expected to change the positive association with HIV incidence but it cannot be excluded that the strength of this association may vary with swabbing sites. Despite this possible underestimation, HR-HPV was the most prevalent sexually transmitted infections in this population. Thirdly, the collection of genital swabs for HPV testing was conducted at the last follow-up visit, on average several months after HIV infection. It is therefore possible that, among the subsets of participants who contracted HR-HPV during

follow-up, some got infected with HPV after HIV acquisition. This will tend to dilute the strength of the association between HPV and HIV. Lastly, HPV lesion detection was not performed in this study.

Several non-exclusive and plausible explanations could account for our findings. Firstly, HIV and HPV are sexually transmitted viruses which share the same behavioral risk factors. However, this association remains strong after controlling for sexual behavioral covariates. Secondly, the results could be partly due to HIV infection facilitating HPV acquisition or HPV reactivation from the basal cell layer in the epithelium. This explanation is unlikely to play a significant role because the men participating in this study were recently infected with HIV and most likely still had an intact immune system. Thirdly, it could be argued that HIV- HPV coinfecting female partners may have shed HR-HPV more intensively than HIV-negative women. Indeed, in the case of a depressed immune system, HPV lesions are more likely to be dysplastic²⁸ and immunodepression can reactivate latent HPV infection.^{12,29,30} However, the fact that the average age of the female partners of our study participants was 3 year older than the median age at first sex in this community, which is about 17³¹, makes this last explanation unlikely: the female partners had their sexual debut on average 3 years earlier, making it unlikely that they already had a depressed immune system due to HIV infection. Fourthly, the findings could indicate that HR-HPV, but not LR-HPV, facilitates HIV acquisition.

There are several arguments in favour of the latter explanation. First, there is strong evidence of a correlation between HIV and HPV statuses, as demonstrated in cross-sectional studies⁷⁻⁹ Secondly, two other longitudinal studies have shown that HPV facilitates HIV acquisition among men having sex with men in the US³² and among women in Zimbabwe.³³ Interestingly, this last study demonstrates a differential effect between HR-HPV and LR-HPV on HIV acquisition. Thirdly, HR-HPVs facilitating HIV acquisition is biologically plausible.

The possibility that HR-HPV could increase the susceptibility to HIV infection was first evoked in 2002.³⁴ The arguments are a) that HR-HPV infection of basal cell epithelia could lead to an active cell-mediated immune response through the recruitment of macrophages and T lymphocytes,^{35,36} which are HIV target cells and may facilitate HIV acquisition, b) genital HPV could simulate cytokines^{36,37} which can increase HIV transcription and replication and c) HPV infection can lead to persisting inflammation and immune system activation.³⁸ In addition, HR-HPV is more likely to result in a persistent infection (versus LR-HPV),³⁹⁻⁴¹ increasing the likelihood of HIV acquisition if there is really HPV-induced immune activation.

While this study cannot give a definite explanation of the association of HPV and HIV incidence, it provides additional evidence on their strong interaction. Further investigations are needed, using for example existing longitudinal data such as those collected during the two other male circumcision trials ^{42,43} or the data collected during the COL-1492 trial ⁴⁴ conducted on female sex workers from South Africa. Testing the hypothesis that HR-HPV facilitates HIV acquisition is a complex endeavor because it requires the demonstration of a causal association, which may only be evidenced through the evaluation of the efficacy of the existing HPV vaccines against HIV acquisition with a randomized controlled trial.

FIGURE CAPTION

FIGURE 1. Distribution of HIV incidence as a function of the number of high-risk human papillomavirus genotypes.

py indicates person-year.

The data for the number of HR-HPV from 4 to 8 have been combined. The error bars represent the 95% confidence interval of the HIV incidence. A 2nd degree polynomial curve has been fitted to the graphics.

FIGURE 2. Distribution of the number of high risk HPV genotypes among the 1683 participants for those with at least one high risk HPV genotype.

The number of participants with any high risk HPV genotype (82.7%, 1391/1683) is not represented on the figure.

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