The epidemiology of HPV and HIV among high-risk women and steady couples in Kigali, Rwanda
Veldhuijzen, N.J.

Citation for published version (APA):

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Factors affecting transmission of mucosal human papillomavirus

Lancet Infectious Diseases 2010;10(12):862-874

Nienke J Veldhuijzen
Peter JF Snijders
Peter Reiss
Chris J Meijs
Janneke H van de Wijgert
ABSTRACT

Human papillomavirus (HPV) is the most common sexually transmitted infection. The effect of HPV on public health is especially related to the burden of anogenital cancers, most notably cervical cancer. Determinants of exposure to HPV are similar to those for most sexually transmitted infections, but determinants of susceptibility and infectivity are much less well established. Gaps exist in understanding of interactions between HPV, HIV, and other sexually transmitted infections. The roles of mucosal immunology, human microbiota at mucosal surfaces, host genetic factors and hormonal concentrations on HPV susceptibility and infectivity are poorly understood, as are the level of effectiveness of some primary or secondary preventive measures other than HPV vaccination (such as condoms, male circumcision, and combination antiretroviral therapy for HIV). Prospective couples studies, studies focusing on mucosal immunology, and in-vitro raft culture studies mimicking HPV infection might increase understanding of the dynamics of HPV transmission.
INTRODUCTION

Infection with human papillomavirus (HPV) is the most common sexually transmitted infection worldwide. The focus of research has been on women because the clinical risk of anogenital (mainly cervical) cancer is much higher in women than in men. HPV research in men has only recently gained momentum as a result of the availability of HPV vaccines, the high burden of anal precancerous lesions in men with HIV, and the recognition that invisible flat penile lesions have an important role in male-to-female transmission.

More than 100 different HPV types have been identified so far. Mucosal HPV types belong to the α genus of papillomaviruses. 15 of the α HPV types have been associated with cervical neoplasms and are therefore classified as high risk, three as probable high risk, and 12 as low risk. 2 The high-risk HPV types are also implicated in vulvar, vaginal, penile, anal, and oropharyngeal neoplasms. 3 High-risk HPV types 16 and 18 cause up to 70% of cervical cancers. 4 Low-risk HPV is causal in development of genital warts. Up to 50% of cases of penile cancer are associated with HPV and HPV 16 is the predominant type. 5,6 Cervical cancer is the third most common cancer in women worldwide, and the most common cancer in women in sub-Saharan Africa, where 85% of cases occur. In 2008, up to 529.000 new cases were detected and 274.000 women died from cervical cancer. 6

Mucosal HPV types infect the basal epithelial cells of the anogenital mucosa via microabrasions in the epithelial lining. 7 Vulval, vaginal, penile, cervical, and anorectal areas are affected. Cervical and anal squamous-cell carcinoma develop at sites of squamous metaplasia; cervicovaginal and anorectal squamous columnar junctions are therefore especially vulnerable to high-risk HPV infection. 8 HPV evades the immune system because its replication does not induce cytolysis, necrosis, or viremia; viral proteins or virions are released in high quantities only in terminally differentiated epithelial cells, which are programmed for natural cell death and therefore remote from immune surveillance. 9 Moreover, HPV inhibits interferon synthesis, 7,10,11 and infection only induces a slow and weak immune response. 12 Nevertheless, 90% of the infections are cleared within 2 years mainly as a result of cell-mediated immune responses directed against early HPV proteins. 13 Seroconversion only occurs in about 60% of women, 14 and men are much less likely than women to have HPV antibodies detected. 15 Although data are scarce, antibodies developed during natural infection do not seem to offer full protection against reinfection, possibly because of low or waning titres. 16,17 By contrast, the available prophylactic HPV vaccines induce high concentrations of neutralising antibodies (at least two logs higher than after natural infection) and immune memory. 18,19 The efficacy of the vaccine against cervical intraepithelial neoplasia (CIN2 or worse) associated with HPV 16 and 18 in women naive for infection is high: 93% (96-1% CI 79-9–98-3) for the bivalent vaccine (HPV 16/18) after 35 months of follow-up and 98% (95% CI 93-3–99-8) for the quadrivalent vaccine (HPV 6/11/16/18) after 42 months of follow-up. 20–23 Vaccine efficacy is, however, much lower in women with prevalent HPV infection. 22,24

Knowledge about transmission dynamics of infectious diseases is needed to define strategies for disease control and to provide input parameters for studies modelling the effect of preventive measures on population. Transmission dynamics are dependent on both pathogen and host factors and are defined by intensity or rate of exposure, susceptibility of a contact person, and duration of
EPIEMIOLOGY

The lifetime risk of cervical HPV infection is up to 80%. Most of these infections (up to 90%) are cleared within 2 years and only a few become persistent. Worldwide HPV prevalence in women with normal cytology is highest in the youngest age groups, below age 25–35 years depending on the study design, and usually declines thereafter. In Africa, the Americas, and Europe, but not in Asia, a second peak is sometimes observed in women older than 45 years. However, other patterns (no decline in older age groups and no second peak) have been reported in some countries (e.g., Nigeria). Worldwide age-adjusted prevalence of HPV in women with normal cytology is estimated at 10–4%, ranging from 8.1% in Europe to 22.1% in Africa.

The prevalence of genital HPV infection in men is not well established and results from studies are difficult to compare because of differences in sampling methods, differences in study population, and poor reporting of the presence or absence of clinical lesions. Prevalence ranges from 3% of the general male population in Spain, up to 70% of attendees of Canadian clinics for sexually transmitted diseases, and 72% of the general male population in Brazil.

HPV incidence is highest in young women and in newly formed heterosexual couples. In most studies, incidence of a group (high-risk or low-risk) or type-specific HPV is assessed in women with no HPV infection at baseline or in women with a different HPV type than the one of interest. Incidence rates for any HPV type range from 9.5 per 100 person-years of follow-up (no CI reported) in a cervical cancer screening population to 22.8 per 100 person-years (95% CI 19.4–26.8) in first-year university students; for high-risk HPV types, 4.8 per 100 person-years (no CI reported) in female drug users to 16.9 per 100 person-years (13.7–20.3) in first-year university students; and for low-risk HPV types 9.9 per 100 person-years (8.1–12.1) in gynaecology clinic patients to 14.9 per 100 person-years (12.5–17.8) in first-year university students. Cumulative incidence after 12 months of follow-up for any HPV infection range from 7.5% up to 56% (table 1). These incidence ranges are similar to those reported for herpes simplex virus type 2 (HSV2) and higher than those for HIV.

Incidence of HPV infection in men is much less well established. In Mexican soldiers, incidence was estimated at 20.4 per 100 person-years (95% CI 15.6–28.7) for any HPV; 14.3 per 100 person-years (9.8–19.9) for high-risk HPV; and 12.7 per 100 person-years (8.8–17.8) for low-risk HPV. The cumulative incidence ranged from 13.8% (8.6–19.0) in Danish soldiers after 6–8 months of follow-up to 62.4% (95% CI 52.6–72.7) in male university students after 24 months of follow-up (table 2).

ESTIMATION OF HPV TRANSMISSION RATES

The transmission potential of HPV infection has mainly been quantified by use of its proxy of group-specific or type-specific HPV concordance in couples. Whereas most studies estimated prevalent concordant infections, one study tried to estimate the overall HPV transmission rate prospectively. In that study, 25 heterosexual couples were followed up for an average of 7.5 months with follow-up visits every 2 months. Samples were obtained from both men and women
from a number of different urogenital sites. The overall HPV transmission rate was estimated to be 58.8 per 100 person-years from penis-to-cervix and 208.8 per 100 person-years from cervix-to-penis. The transmission rate for high-risk HPV was estimated to be 28.8 per 100 person-years for penis-to-cervix and no estimate was provided for cervix-to-penis. HPV type-specific transmission values could not be calculated because of the small sample size.\(^{62}\) HPV concordance in cross-sectional couple studies ranges from 3% to 37%.\(^{62}\) This wide range could be attributable to differences in sampling techniques (especially in men), HPV assays used, and in the definition of concordance (group-specific or type-specific). Another important variable is the presence of clinically apparent HPV-related lesions in the partner: HPV concordance values are higher when such lesions are present, which might be due to increased viral loads.\(^{62,63}\) For example, type-specific concordance in HPV-positive couples of whom women had cervical intraepithelial neoplasia lesions was 58%.\(^{62}\) Use of cross-sectional couple concordance as a proxy for transmission probability is not ideal because current concordance, especially of common HPV types, could reflect transmission in previous or concurrent relationships. A mathematical simulation model showed a probability of per-coital-act transmission of any HPV of 5–100% (median 40%).\(^{64}\) A longitudinal couple study in Montreal, Canada, calculated an overall transmission probability of 42% (95% CI 36–47) per partnership and 0.80% (0.6–1.0) per act.\(^{14,65}\)

### Table 1: Factors associated with HPV acquisition in women in multivariable analyses

<table>
<thead>
<tr>
<th>Period</th>
<th>Population</th>
<th>Age (years)</th>
<th>HPV</th>
<th>Incidence T</th>
<th>Risk factors</th>
<th>Protective factors</th>
<th>No association</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (166)(^{1})</td>
<td>1993-1994</td>
<td>University (USA)</td>
<td>20</td>
<td>Any</td>
<td>Negative (n=199)</td>
<td>1 year (21%); 2 years (40%); 3 years (45%); 4 years (36%)</td>
<td>Other age; present partner in school</td>
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<td></td>
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<td></td>
<td>Higher parity; increasing alcohol intake; history of sex with larger number of sex partners; past history of cervical dysplasia; history of vaginal sex; increasing number of male partner’s LTSP</td>
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<td></td>
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<td>Current use of oral contraceptives</td>
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<td></td>
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<td></td>
<td></td>
<td>History of marijuana use; LTSP</td>
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<td></td>
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<td></td>
<td></td>
<td>Age, parity (dip and/or top) to HPV16 and/or number of different HPV types observed in previous visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (200)(^{2})</td>
<td>1993-1994</td>
<td>University (USA)</td>
<td>20</td>
<td>Any</td>
<td>Positive (n=201)</td>
<td>1 year (17%); 2 years (50%); 3 years (77%); 4 years (96%)</td>
<td>No association</td>
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<td></td>
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<td></td>
<td>Increasing number of sex partners (previous 30 months) and relationship with regular partner</td>
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<td></td>
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<td></td>
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<td>Age, duration of sex partner relationship; history of sexual debut</td>
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<td></td>
<td></td>
<td></td>
<td>Age, parity (dip and/or top) to HPV16 and/or number of different HPV types observed in previous visits</td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td>Other age; age at sexual debut; age at sexual debut; number of sexual partners longer than 5 years ago</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (200)(^{2})</td>
<td>1993-1997</td>
<td>Physiological sex (Canada)</td>
<td>327</td>
<td>M/F</td>
<td>Negative (n=235)</td>
<td>1 year (21%); 2 years (40%); 3 years (45%); 4 years (36%)</td>
<td>No association</td>
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<td></td>
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<td></td>
<td>Increasing number of current and/or number of sex partners; history of sexual debut; history of smoking; history of marijuana use; history of cervical dysplasia; history of cervical cancer</td>
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<td></td>
<td>Age, parity (dip and/or top) to HPV16 and/or number of different HPV types observed in previous visits</td>
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<td>Other age; age at sexual debut; age at sexual debut; number of sexual partners better than 5 years ago</td>
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<tr>
<td>No. (200)(^{2})</td>
<td>1995-1997</td>
<td>National and child health program (Shaq)</td>
<td>195</td>
<td>Male</td>
<td>Negative (n=187)</td>
<td>1 year (21%); 2 years (40%); 3 years (45%); 4 years (36%)</td>
<td>No association</td>
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<td></td>
<td>Increasing cumulative number of sex partners last 12 months; increasing number of sex partners’ age at sexual debut; history of cervical dysplasia; history of sexual debut; parity (top or bottom) to HPV16 and/or number of different HPV types observed in previous visits</td>
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<td></td>
<td></td>
<td>Other age; age at sexual debut; age at sexual debut; number of sexual partners better than 5 years ago</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (200)(^{2})</td>
<td>1995-1997</td>
<td>University students (USA)</td>
<td>192</td>
<td>Any</td>
<td>Negative (n=192)</td>
<td>1 year (21%); 2 years (40%); 3 years (45%); 4 years (36%)</td>
<td>No association</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Increasing cumulative number of sex partners last 12 months; increasing number of sex partners’ age at sexual debut; history of cervical dysplasia; history of sexual debut; parity (top or bottom) to HPV16 and/or number of different HPV types observed in previous visits</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Other age; age at sexual debut; age at sexual debut; number of sexual partners better than 5 years ago</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continues on next page
<table>
<thead>
<tr>
<th>Period</th>
<th>Population</th>
<th>Age (mean)</th>
<th>HPV</th>
<th>Baseline HPV status</th>
<th>Incidence</th>
<th>Risk factors</th>
<th>Prophylactic</th>
<th>No association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manila, [2004][17] 1995-1996</td>
<td>Screaming (Caloocan)</td>
<td>32.3 (median)</td>
<td>Any</td>
<td>Negative (n=3,015)</td>
<td>1 year: 9%; 3 years: 18%; 5 years: 28%</td>
<td>Increasing number of lifetime sexual partners; early sexual debut; history of HPV infection; history of sexually transmitted diseases; history of alcohol use; increasing number of sexual partners</td>
<td>Older age</td>
<td>Patty et al.</td>
</tr>
<tr>
<td>Sulangan, [2005][18] 2003-2004</td>
<td>Population based (Iligan)</td>
<td>20 (median)</td>
<td>HR</td>
<td>Negative (n=1,715)</td>
<td>1 year: 2% (21-26)</td>
<td>Self-reported history of sexual abuse; female partner age; history of pregnancy; HPV positive at enrolment</td>
<td>Other age</td>
<td>Patty et al.</td>
</tr>
<tr>
<td>Fukuoka, 2004-2005</td>
<td>HPV prevalence (Japan)</td>
<td>27</td>
<td>Any</td>
<td>Negative (n=430)</td>
<td>1 year: 11% (5-19)</td>
<td>Self-reported history of sexual abuse; female partner age; history of pregnancy; HPV positive at enrolment</td>
<td>Older age</td>
<td>Patty et al.</td>
</tr>
<tr>
<td>Nelson, 2005-2006</td>
<td>Population based (Zimbabwe)</td>
<td>Range: 20-29</td>
<td>HR</td>
<td>Negative (n=240)</td>
<td>2 years: 17% (12-14)</td>
<td>Self-reported history of sexual abuse; female partner age; history of pregnancy; HPV positive at enrolment</td>
<td>Other age</td>
<td>Patty et al.</td>
</tr>
<tr>
<td>Chris [2007]</td>
<td>Population based (Thailand)</td>
<td>45 (median)</td>
<td>Any</td>
<td>Negative (n=913)</td>
<td>3 years: Age 30; 4 years: Age 20-29</td>
<td>Self-reported history of sexual abuse; female partner age; history of pregnancy; HPV positive at enrolment</td>
<td>Older age</td>
<td>Patty et al.</td>
</tr>
</tbody>
</table>

LTP: life-time sex partner, STD: sexually transmitted disease, HPV: human papillomavirus, HPV-2: herpes simplex virus 2, VLP: viral-like particle, *HPV baseline status is negative if participants were free of any HPV type at baseline; positive refers to prevalent HPV types at baseline; both if these groups are combined. Incidence presented as cumulative incidence N. (95% CI). [If reported] unless stated otherwise

**FACTORS INFLUENCING EXPOSURE**

Mucosal HPV infections are transmitted through direct skin-to-skin contact and the most common route of transmission is through penetrative sex. Exposure is therefore determined by well known risk factors for most sexually transmitted infections such as number of life-time sexual partners, recent or present number of sexual partners, frequency of sex or other intimate skin-to-skin contact, and the sexual histories and behaviours of sexual partners. Alcohol use is also associated with HPV infection, most probably because of its association with unsafe penetrative sex. Non-penetrative sex is a less common route of transmission. Self-reported virginal women engaging in non-penetrative sexual contacts had a 2-year cumulative HPV incidence of 7.9%. Anogenital HPV infection in children is believed to be caused by sexual abuse in 3–35% of cases, but, particularly those involving low-risk types HPV 6 and 11, can also be explained by transmission during pregnancy and delivery, or via contact with contaminated objects or surfaces.

Effectiveness of condom use in reduction of HPV acquisition is not proven, but an increasing number of studies show a trend towards a protective effect. This effect might be sex-dependent: studies show a more pronounced effect on male HPV acquisition than on female HPV acquisition. The data are difficult to interpret because few studies were specifically designed to assess condom use, and self-reports on condom use are typically unreliable. Moreover, the frequency of condom use is classified differently depending on the study, and the risk of HPV exposure can never be fully quantified. One longitudinal study aiming to assess condom...
effectiveness in 82 female university students initiating sexual intercourse just before or during the study period reported a reduced risk of cervical and vulvovaginal HPV acquisition with consistent condom use versus condom use in less than 5% of sex acts—adjusted hazard ratio (HR) 0.3 (95% CI 0.1–0.6). Other prospective studies included condom-use as one of several risk factors but most did not find a protective effect on HPV acquisition (Tables 1 and 2). Results from studies in couples in whom one partner had anogenital lesions related to HPV (flat penile lesions or cervical lesions) have shown a positive effect of condom use on lesion regression.77,78

Female condoms could be thought to protect women better from HPV acquisition than male condoms because they cover a larger mucosal area, but this topic has not been studied so far.

Table 2: Factors associated with HPV acquisition in men in multivariable analyses

<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
<th>Population</th>
<th>Age (years)</th>
<th>Specimen</th>
<th>HPV type</th>
<th>Baseline HPV statusa</th>
<th>Incidencea</th>
<th>Risk factors</th>
<th>Protective factors</th>
<th>Condom use</th>
<th>No association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Álvarez (2005)</td>
<td>2003–2005</td>
<td>Soldiers (Mexico)</td>
<td>Median 23</td>
<td>Glans + shaft + urethral meatus</td>
<td>Any</td>
<td>Negative</td>
<td>6.4 months; 14% (95% CI 3.6–24.5%)</td>
<td>Older age, 3 or more sex partners</td>
<td>Smoking, Chlamydia Trachomatis and Neisseria gonorrhoeae, age, condoms use</td>
<td>Age, socio-economic status, LTPH, circumcision</td>
<td></td>
</tr>
<tr>
<td>Parkes (2007)</td>
<td>2005–2006</td>
<td>University students (USA)</td>
<td>18</td>
<td>Glans + shaft + scrotum</td>
<td>Any</td>
<td>Negative</td>
<td>24.5% (95% CI 20.4–29.6%); 24.5% (95% CI 20.4–29.6%)</td>
<td>New recent sex partners, history of smoking</td>
<td>Age, socio-economic status, LTPH, history of vaccbung</td>
<td></td>
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</tr>
<tr>
<td>Lu00H (2005)</td>
<td>2005–2005</td>
<td>Population-based (USA)</td>
<td>30</td>
<td>Glans + shaft + scrotum</td>
<td>Any</td>
<td>Negative</td>
<td>12.2% (95% CI 7.4–17.9%); 12.2% (95% CI 7.4–17.9%)</td>
<td>Smoking, circumcision, age, sex debut</td>
<td>LTPH, Higher education</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TS = life-time sex partners. * HPV baseline status as explained in Table 1. † Incidence presented as cumulative incidence (95% CI, if reported) unless stated otherwise.

**FACTORS INFLUENCING HOST SUSCEPTIBILITY**

Non-modifiable or partially modifiable host factors

All sexually active men and women are susceptible to genital HPV infection. Incidence and prevalence peak at young age because of both behavioural and biological factors. Young people are exposed to HPV more often because of their sexual behaviour, and young women are more vulnerable than older women because the transformation zone at that age is located on the ectocervix (cervical ectopy).79

Host genetic factors have been implicated in persistence of oncogenic HPV infection and in cervical carcinogenesis, but their effect on host susceptibility for HPV has not been sufficiently studied.80,81 A series of case-control studies in women82,83 investigated the effect of polymorphisms of MBL2, a gene for mannose-binding lectin that is essential for innate immunity,
on HPV acquisition. The results are difficult to interpret because they are inconsistent. Furthermore, the cases studied included women with cervical precancerous lesions, so the effects of MBL2 polymorphisms on HPV acquisition and persistence were hard to distinguish.32,83

Impaired cellular immunity—eg, in patients with renal transplant35,85 and HIV-positive individuals—is associated with increased incidence and persistence of HPV infection and HPV-related diseases. HIV and HPV share transmission routes and risk behaviour, but multiple studies36 have established an increased prevalence of HPV in individuals infected with HIV independent of sexual behaviour. Prospective studies have assessed the incidence, persistence, and clearance of HPV in HIV-positive women compared with HIV-negative women (table 3). HPV incidence and persistence are higher in HIV-positive women (measures of effect ranging from 2.2 to 8.8 for incidence39,88–90,91 and from 1.3 to 7.5 for persistence35,87,92,93) and clearance is lower (0.3–0.8) than in HIV-negative women.38,90,91,93–95 All associations become stronger with increasing immunodeficiency (low CD4 count or high plasma HIV viral load). Furthermore, HIV-positive individuals are more likely to present with multiple HPV infections than are HIV-negative individuals.97,98 However, evidence is accumulating that HPV incidence and persistence have not decreased since the introduction of combination antiretroviral therapy (cART), and the effect of this therapy on the development of cervical lesions in HIV-positive women is unclear.99,100,101 CART does restore immune function but evidence that it increases cervical lesion regression or decreases lesion progression in HIV-infected women is not consistent.100 Although some studies found an increased regression of cervical lesions in HIV-infected women using cART, others did not.101–104 Moreover, the incidence of anal cancer in HIV-positive men, also associated with high-risk HPV infection, has increased since the use of cART. Therefore, this therapy seems to have no effect on the development of anal lesions.100

HPV infection might also be a risk factor for HIV acquisition.105–108 If high-risk HPV infection does increase risk of HIV acquisition, HPV vaccination could have an effect on the HIV epidemic.

Modifiable host factors

Several modifiable host factors are potentially associated with susceptibility to HPV infection. Some of these factors, such as use of hormonal contraception, parity, smoking, and concurrent sexually transmitted infections, have been studied predominantly in women in the context of cervical carcinogenesis. Others, such as imbalanced vaginal flora and having an uncircumcised male partner, are just emerging. A few (eg, vaginal practices) have not yet been studied sufficiently. Condom use and circumcision are among the most studied factors associated with HPV infection in men.

Long-term use of oral contraceptives has been associated with an increased risk of cervical cancer.106 However, the role of oral contraceptive use in HPV acquisition is less clear.107,108 Oral contraception promotes cervical ectopy, which could provide a biologically plausible explanation for increased HPV acquisition. Several factors associated with HPV acquisition are also associated with oral contraceptive use, such as age, sexual behaviour, and smoking. These factors are therefore important sources of confounding. Findings from one prospective study77 in female university students showed a significantly increased risk of HPV incidence associated with present use of oral contraceptives after controlling for sexual behaviour, and smoking status—adjusted HR 1.4 (95% CI 1.01–1.8). Results from another prospective study, however, showed a protective
effect in multivariate analysis—adjusted HR 0·49 (0·28–0·86)\(^{17}\)—and other studies reported no significant association.\(^{11,42,46,113}\) Several cross-sectional analyses also reported inconclusive results, ranging from no significant association with use of oral contraceptives to increased odds of high-risk HPV infection.\(^{112–114}\)

The role of parity in the acquisition of HPV is also complicated by confounding factors such as sexual and reproductive behaviour and age. Results from a large prospective cohort study\(^{41}\) showed a protective effect of higher parity on HPV incidence after control for various factors associated with sexual risk behaviour, such as oral contraceptive use, age at first intercourse, and recent new sexual partners—for any HPV, adjusted odds ratio (OR) 0·6 (95% CI 0·4–0·9). However, most studies to date do not indicate an influence of parity on risk of HPV acquisition.\(^{115,47}\) By contrast, increasing parity has been associated with cervical carcinogenesis.

As with oral contraceptive use and alcohol use, tobacco smoking is associated with increased sexual risk behaviour complicating the ascertainment of an association between smoking and HPV acquisition. Most studies focused on the role of smoking in cervical carcinogenesis (finding a positive association)\(^{115,116}\) rather than HPV acquisition. Smoking and HIV infection increased prevalence and incidence of HPV acquisition independently from one another in HIV-positive and HIV-negative women.\(^{117}\) Although the strength of the association between smoking and HPV acquisition was similar in HIV-infected (HR 1·33, 95% CI 1·10–1·60) and uninfected women (HR 1·62, 95% CI 0·88–2·96), statistical significance was not reached in HIV-uninfected women, possibly because of insufficient statistical power. Smoking is thought to increase acquisition or reactivation of HPV because of its immunosuppressive effect on innate and adaptive immunity.\(^{118}\)

In analogy with susceptibility to HIV infection, people with other sexually transmitted infections could have an increased susceptibility to acquisition or persistence of HPV independent of sexual behaviour. The postulated mechanism is that microabrasions in the epithelial lining, perhaps as a result of inflammation, increase access to basal cells, which are the target cells for HPV. Studies of associations between HPV and other sexually transmitted infections in women thus far have focused on the role of \(C\) \textit{trachomatis} or HSV2 co-infection as a cofactor in HPV persistence and cervical carcinogenesis, and results have shown increased HPV persistence in co-infected women.\(^{119–123}\) Results from one prospective study in women showed an increased risk on HPV acquisition in patients with previous laboratory detection of genital co-infections (\(C\) \textit{trachomatis}, \textit{Neisseria gonorrhoeae}, \textit{Trichomonas vaginalis}, or syphilis) and with HSV2 seropositivity, but another study did not show an association with concurrent \(C\) \textit{trachomatis}.\(^{42,49}\) Laboratory diagnosed \textit{N gonorrhoeae} or \textit{C trachomatis} was associated with HPV detection in men in one study.\(^{107}\) More studies have investigated the role of vaginal flora imbalances and HPV. So far, only one prospective study has been published,\(^{52}\) which reported an association between bacterial vaginosis (diagnosed by Nugent criteria) and any HPV incidence (adjusted HR 1·41, 95% CI 1·25–1·59) and prevalence (adjusted OR 1·17, 95% CI 1·08–1·27) in a multiethnic, HIV-positive and HIV-negative American population adjusted for age, race, number of present sexual partners, CD4 count, and infection of \(T\) \textit{vaginalis}. The reverse was also reported: HPV was a risk factor for incident bacterial vaginosis. Results from cross-sectional studies are inconsistent. In the National Health and Nutrition Examination Survey in the USA,\(^{124}\) bacterial vaginosis was associated with viral sexually transmitted infections (including HPV) in univariate analyses.
### Table 3: Association between HIV status and HPV incidence, persistence and clearance among women

<table>
<thead>
<tr>
<th>Country</th>
<th>Period</th>
<th>Population</th>
<th>HAART</th>
<th>HIV</th>
<th>Baseline prevalence (%)</th>
<th>Incidence</th>
<th>Persistent*</th>
<th>Clearance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (1997)**</td>
<td>USA</td>
<td>1991-8</td>
<td>HIV reg</td>
<td>HIV pos</td>
<td>No</td>
<td>Any</td>
<td>31%</td>
<td>69%</td>
</tr>
<tr>
<td>Alford (2001)**</td>
<td>USA</td>
<td>1993-94</td>
<td>HIV reg</td>
<td>HIV pos</td>
<td>No</td>
<td>HIV</td>
<td>28%</td>
<td>73%</td>
</tr>
<tr>
<td>Silverberg (2001)**</td>
<td>USA</td>
<td>1993-95</td>
<td>HIV reg</td>
<td>HIV pos</td>
<td>No</td>
<td>Any</td>
<td>27%</td>
<td>54%</td>
</tr>
<tr>
<td>Dene (2003)**</td>
<td>Fury</td>
<td>1987-96</td>
<td>HIV reg</td>
<td>HIV pos</td>
<td>Yes</td>
<td>(100%)</td>
<td>Any</td>
<td>43%</td>
</tr>
<tr>
<td>Moscicki (2004)**</td>
<td>USA</td>
<td>2001</td>
<td>HIV reg</td>
<td>HIV pos</td>
<td>Yes</td>
<td>(100%)</td>
<td>Any</td>
<td>73%</td>
</tr>
<tr>
<td>Watts (2005)**</td>
<td>USA</td>
<td>1994-95</td>
<td>HIV reg</td>
<td>HIV pos</td>
<td>No</td>
<td>Any</td>
<td>45%</td>
<td>Reference (OR: 1.11)</td>
</tr>
<tr>
<td>Kauril (2006)**</td>
<td>USA</td>
<td>Not reported</td>
<td>HIV reg</td>
<td>HIV pos</td>
<td>No</td>
<td>Any</td>
<td>Reference (OR: 2.00)</td>
<td></td>
</tr>
<tr>
<td>Fontaine (2009)**</td>
<td>Canada</td>
<td>1993-2002</td>
<td>HIV reg</td>
<td>HIV pos</td>
<td>Yes</td>
<td>(100%)</td>
<td>HPV</td>
<td>Reference (OR: 1.01)</td>
</tr>
</tbody>
</table>

Only prospective studies including both HIV positive and HIV negative women; OR=odds ratio. HR=hazard ratio. *Adjusted hazard ratio. **Reference group: HIV negative women. †-Strickler et al** report HR for incidence and persistence by CD4 count and HIV viral load with the same cohort. ‡ Adjusted for study site and risk behaviour for sexual and injection drug use. § Persistence analysis only, cohort restricted to HPV positive women. # Adjusted for HAART group, multiple infections, age, parity, type of contraception, current cigarette smoking, commercial sex worker, new partner in previous 4 months.

However, after controlling for sexual behaviour, the association was only significant for HSV1 or HSV2. Results from a combined clinic-based and community-based study in Brazil showed some evidence for an association between bacterial vaginosis and prevalent high-risk HPV infection after control for behavioural risk factors (adjusted prevalence rate ratio 1.5; p=0.06). Results from a small cross-sectional study in pregnant women in Brazil showed a significant association between HPV prevalence and bacterial vaginosis (diagnosed by Amsel criteria) in univariate analysis (p<0.007), but no multivariate analyses were done. More consistent results were reported for the association between bacterial vaginosis and cervicointraepithelial lesions. These complex relations between the vaginal microenvironment and viral sexually transmitted infections, and between those infections themselves, need to be better understood. Whether vaginal practices are associated with HPV acquisition via changes of the vaginal microenvironment also remains to be assessed.

A protective effect of male circumcision on male HPV prevalence was reported in two randomised controlled trials. These findings added valuable knowledge to the inconclusive results from observational studies, both trials were designed to study the association between male circumcision and HIV acquisition in men and showed a reduced risk of HIV acquisition in circumcised men. The association between male circumcision and high-risk HPV prevalence was assessed cross-sectionally after 21–24 months of follow-up. The South African trial reported a prevalence rate ratio of 0.66 (95% CI 0.51–0.86) and the Ugandan study of 0.56 (0.37–0.85). These cross-sectional analyses can, however, not differentiate between reduced prevalence as a result of reduced acquisition or of increased clearance rate. Circumcised men were more likely to clear HPV infection (adjusted HR 3.1, 95% CI 1.2–8.2) than were uncircumcised men in a prospective study of 285 men.
in which no difference in acquisition was noted [0-8, 95% CI 0·4-1-9]). Similar results were obtained from a Hawaii cohort study, in which HPV infection took longer to clear in uncircumcised men [Risk ratio (RR) 0·70; p=0·001]. In Uganda, circumcision was associated with decreased acquisition of multiple high-risk HPV types in HIV-negative (RR 0·41, 95% CI 0·23-0·75) and HIV-positive men (RR 0·40, 95% CI 0·19-0·84), and increased clearance in only HIV-negative men (RR 1·36, 95% CI 1·13–1·63).133,134

The effect of male circumcision on female HPV acquisition, other than through a lower HPV prevalence in circumcised men, remains to be established. Whether circumcised HPV-positive men are less infectious than uncircumcised HPV-positive men is unknown; although this does not seem to be the case for HIV. A randomised controlled trial assessing the effect of male circumcision on risk of HIV transmission from HIV-infected men to their female sexual partners was stopped early for futility (adjusted HR 1·49, 95% CI 0·62–3·57).136 If concurrent sexually transmitted infections are associated with HPV acquisition, male circumcision could also reduce HPV prevalence via a demonstrated reduced prevalence of other sexually transmitted infections in circumcised men and their female partners.138

FACTORS AFFECTING INFECTIVITY

Some studies suggest selective transmission of different HPV types with HPV 16 being the most readily transmitted type. Genomic variation within HPV types has been linked with pathogenic differences but not with transmissibility. This link has best been shown for HPV 16, for which non-European variants have consistently been associated with an increase of up to nine times in the risk of cervical cancer or high-grade lesions compared with European variants.90

Genital HPV viral load is one host factor likely to have a central role in infectivity. Concordance is higher in couples in which one of the partners has a high genital viral load than in couples with low viral load. High viral load is associated with an increased presence of clinical lesions and concordance rates are higher in couples in which one partner has HPV-associated anogenital lesions. Another factor repeatedly associated with higher genital HPV viral load is HIV infection.90,139

Winer and colleagues attempted to characterise behavioural risk factors for high HPV viral loads in incident infections, but the researchers could not do so because of a small number of HPV endpoints. More than one new sex partner in the past 8 months was the only variable that was significantly associated with increased viral loads.

FACTORS INFLUENCING PERSISTENCE

The definition of HPV persistence is not consistent in the scientific literature. A meta-analysis on the association of persistent HPV infection and cervical neoplasia reported that 78% of studies defined it as having two or more HPV-positive visits and 20% of studies defined it as having three or more HPV-positive visits, with a medium interval between HPV tests of 6 months (range 2–72 months). The minimum duration of persistent HPV infection was 6–12 months in 45% of the
Viral characteristics that have been associated with persistence of infection include HPV type and variant, concomitant infection with other types, and viral load. High-risk HPV persists longer than low-risk HPV, and of the high-risk types, those related to HPV 16 (HPV 16, HPV 31, HPV 33, HPV 35, HPV 52 and HPV 58) persist the longest. Non-European variants of HPV 16 and 18 tend to persist longer than do European variants of HPV 16 and 18. The duration of infection is not normally distributed, but skewed to the right, resulting in the majority of infections persisting for longer periods. Prevalent infections might over-represent the right tail of the duration distribution, with a longer clearance rate than for incident infections. A cohort study in women in Brazil estimated a median duration of incident high-risk HPV infection of 6.5 months (95% CI 6.2–8.6) compared with prevalent high-risk HPV infections of 8.2 months (8.0–9.2). The median duration of incident low-risk HPV was 6.2 months (95% CI 6.0–6.7) and for prevalent infections 6.2 months (4.5–8.0). Other studies also found shorter durations of low-risk HPV infections compared with high-risk HPV infections. Whether multiple-type infections increase the likelihood of persistent infection is unclear because of conflicting results. Finally, one study estimated the median time to clearance of prevalent HPV infection in men. For any prevalent HPV-type infection median time to clearance was 5.9 months, 5.8 months for high-risk HPV, and 6 months for low-risk HPV (no CIs reported).

Several host factors have been associated with HPV persistence including host genetics, immune status, hormones, tobacco smoking, parity, and presence of other sexually transmitted infections such as HIV, HSV2, and C trachomatis.

CONCLUSION

HPV is a ubiquitous sexually transmitted infectious pathogen with high probability of transmission. In developed countries the burden of HPV for health services is related to identification and management of precancerous lesions, and in developing countries burden is caused mainly by anogenital cancers, of which cervical cancer is the most prevalent.

Exposure to HPV is determined by well known risk factors for most sexually transmitted infections. Determinants of susceptibility and infectivity are much less well established. Gaps exist in the understanding of host genetic factors, hormone concentrations, human microbiota at susceptible mucosal surfaces, and mucosal immunology on host susceptibility and infectivity. Interactions between HPV, HIV, other sexually transmitted infections, and human microbiota are incompletely understood; and the effectiveness of some preventive measures is unknown (i.e., male and female condoms and male circumcision in the case of primary prevention, and combination antiretroviral therapy in the case of primary and secondary prevention). Finally, standardised sampling methods and measurements are needed to study infection in men and to define persistence. The effect of HPV vaccination on the epidemics of HIV (and HSV2) deserves
further study.

The gaps in understanding are best addressed in prospective epidemiological studies enrolling newly formed young couples initiating sexual intercourse at the time of enrolment or during the study, combined with laboratory studies, particularly in the specialty of mucosal immunology. Enrolment of such couples is challenging, as was recently reviewed by Rowhani and colleagues.\(^{148}\) An alternative would be to follow couples that are HPV discordant by PCR analysis at baseline and in which the susceptible partner is negative for HPV antibodies. Efforts are underway to validate and standardise genital specimen collection and mucosal immunology assays.\(^{149,150}\) Chow and colleagues\(^{151}\) developed an organotypic raft culture system for HPV that allows in-vitro production of infectious particles and that might offer new possibilities in the future to study host-viral interactions in HPV in vitro.

In conclusion, although programmes of cervical cancer screening and vaccination have reduced and will reduce morbidity and mortality related to HPV, more can be done to reduce the burden of infection in both women and men, and to decrease the effect that HPV might have on the epidemics of HIV and other sexually transmitted infections.
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