HPV Vaccination to Prevent HIV Infection: Time for Randomized Controlled Trials

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Despite many years of rigorous evaluation of a variety of interventions, HIV incidence rates in parts of Africa remain unacceptably high. A recent review identified 37 randomized controlled trials testing interventions to reduce HIV incidence.[1] Except for 3 randomized controlled trials of male circumcision[2–4] and 1 trial of syndromic treatment of sexually transmitted diseases,[5] and, recently, 1 trial of a vaginal microbicide,[6] no significant reductions in HIV incidence were observed. In some trials of vaginal microbicides, trial participants in the active treatment arm actually had increased HIV incidence rates.[7] Trials with candidate vaccines have been equally disappointing.[8] A recently completed trial of a prime-boost strategy conducted in Thailand showed statistically significant, but limited, protection against HIV.[9] Nevertheless, even vaccine optimists think that a preventive HIV vaccine is many years away.

Sexually transmitted infections (STIs) were identified as important cofactors for HIV transmission early in the epidemic.[10,11] Many prospective observational studies showed that the presence of ulcerative and nonulcerative STIs increased the likelihood of HIV transmission.[10,11] Several interventions were based on this observation including mass treatment with antibiotics,[12] improved syndromic management of STIs,[5,13] and herpes simplex virus (HSV)-2 suppressive treatment.[14] Null findings of these interventions should be interpreted with caution. Failure to show an effect does not necessarily mean that the STI is not causally associated with HIV. As Barnabas and Wasserheit highlight,[15] the stage of the HIV epidemic in which an intervention trial is conducted may significantly influence observed efficacy. Another possible reason for the failure of these trials to demonstrate efficacy is that the intervention may not have adequately controlled the STI or its biologic effects.

HPV OBSERVATIONAL STUDIES

One STI has not received much attention in this regard, although it is highly infectious and the most prevalent STI: the human papillomavirus (HPV). Cross-sectional studies have shown that HIV infected persons harbor HPV infections more often than HIV-negative subjects. Cervical cancer, which is caused by oncogenic HPV, has been an AIDS defining condition since 1993.[16] Interestingly, recent reports from abstract presentation[17] and peer reviewed publications[18–23] indicate that HPV infection may increase the risk of HIV acquisition in men and women.

Chin-Hong et al. were the first to report an association between prevalent HPV infection and subsequent risk of HIV acquisition. The investigators prospectively studied 1409 HIV-negative men who had sex with men in the United States who acknowledged high risk sexual behaviors for HIV acquisition. With 4375 person-years of follow-up, the risk for HIV seroconversion was 3 times higher (hazard ratio, 3.5 [1.2–10.6]) among men with multiple HPV infections at the anal canal compared with men with no anal HPV infections. To control for potential confounding factors, the investigative group adjusted their analyses for sexual activity, substance use, occurrence of several STIs, and demographic variables.[19] However, HSV-2 status was not considered in these analyses.

Recently, there have been 2 reports of the association between genital HPV infection and HIV acquisition among heterosexual men participating in randomized trials of adult male circumcision in southern Africa. Auvert et al. studied the incidence of HIV among 1683 men enrolled in the Orange Farm circumcision trial.[18] After controlling for oncogenic-HPV status, nononcogenic-HPV status was not associated with HIV incidence (adjusted incidence rate ratio: 1.13, 95% confidence

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interval [CI]: 0.40–3.16; $P = 0.82$). HIV incidence was, however, significantly higher among men positive for oncogenic HPV types (adjusted incidence rate ratio = 3.76, 95% CI: 1.83–7.73; $P = 0.001$) and increased linearly with increasing numbers of multiple oncogenic HPV types ($P = 0.0074$) after controlling for sexual behavior. However, the results of this study are difficult to interpret as the exposure status (HPV infection) was established at the same time as the outcome (HIV infection).

Nested within a circumcision trial in Kenya where a strong protective effect of circumcision was noted, Smith et al. examined HIV incidence among 1101 uncircumcised and 1067 circumcised men over a 42-month follow-up period. After adjusting for circumcision status, HSV-2 serostatus, and sexual and sociodemographic risk factors, men with penile HPV infection of any type at enrolment were more likely to acquire HIV compared with men with no HPV infection (hazard ratio 1.8, [95% CI 1.1–2.9]; $P = 0.03$). In analyses stratified by circumcision status, both high risk and low risk HPV types appeared to confer high HIV acquisition, although these analyses did not reach statistical significance.[20]

Adding strength to the observation that HPV infection may increase risk of HIV acquisition, 4 reports of this association have now been reported from studies conducted among women.

Auvert et al. studied HIV seroconversion in a subset of 104 South African female sex workers who participated in a randomized controlled trial of a microbicide. HIV acquisition was significantly associated with oncogenic HPV infection (adjusted rate ratio [RR], 1.5; 95% CI, 1.1–2.1; $P = 0.025$) but not with nononcogenic HPV infection (adjusted RR, 0.81; 95% CI, 0.58–1.1; $P = 0.23$). Compared with oncogenic HPV negative participants, women who were infected with 2 or more oncogenic HPV genotypes were significantly more likely to acquire HIV infection (adjusted RR, 3.4; 95% CI, 1.2–9.1; $P = 0.018$).[17] However, adjustment for HSV-2 status and other STIs was not conducted.[17]

Veldhuijzen et al. studied HIV incidence among a cohort of 366 initially HIV-negative high-risk women (mostly sex workers) in Kigali, Rwanda.[22] In a median period of 16.6 months between study visits, 10 seroconversions were observed. Women who seroconverted were significantly more likely (odds ratio [OR] = 4.9 [95% CI 1.2–19.7]) to have any oncogenic HPV vaginal infection at baseline compared with women who did not seroconvert. However, there was no consideration for demographic variables, sexual behavior, or other STIs in these analyses.

In a study from Zimbabwe, Smith-McCune et al. followed 2040 women for a median of 21 months testing quarterly for 29 HPV types at the cervix and for HIV antibodies.[23] After adjustment for STIs, including HSV-2, and other risk factors, detection of any recent oncogenic HPV (adjusted hazard ratio 1.96, [95% CI 1.16–3.30]) or recent nononcogenic HPV infection (adjusted hazard ratio 1.70, [95% CI 1.02–2.85]) was associated with increased rates of HIV acquisition.[23] Strikingly, when the investigators examined associations between individual HPV types and HIV acquisition, they observed significantly increased risk associated with HPV31 and HPV70, types not included in current vaccines. Recent HPV16 or 18 infections, types targeted by currently licensed vaccines, were not significantly associated with acquisition of HIV infection. In an analysis examining associations between persistent or nonpersistent oncogenic and nononcogenic grouped HPV infections and risk of HIV acquisition, nonpersistent HPV infections were associated with elevated HIV risk. In contrast, persistent HPV infections were not associated with HIV risk.

Finally, Averbach et al. examined HIV incidence among women in Zimbabwe who were enrolled in a large multicenter cohort study examining the effect of hormonal contraception on HIV acquisition.[21] In a nested case–control analysis of 145 cases and 446 controls, an increased risk of HIV acquisition was observed (adjusted OR, 2.4; 95% CI: 1.5–4.0) among women with prior cervical HPV infection compared with those without preceding HPV infection, after adjustment for behavioral and biologic risk factors. This increased risk of HIV acquisition was observed for women with any oncogenic HPV infection (OR = 2.3, 95% CI: 1.4–3.9) as well as for women with nononcogenic HPV types only (OR = 2.8, 95% CI: 1.3–5.9). The investigators observed a dose-response effect: the higher the number of HPV types found during the previous visit, the higher the odds of HIV acquisition (up to an OR of 5.6 (95% CI: 2.5–12.9) for those infected with 4 or more HPV types). Similar to findings from the study of Smith-McCune et al.,[23] the authors observed that loss of detection of at least one HPV type (i.e., nonpersistent HPV) was significantly associated with subsequent HIV acquisition (OR, 5.4; 95% CI: 2.9–9.9).

These prospective studies suggest that cervical, anal, and/or penile infection with oncogenic and nononcogenic HPV types may increase the risk of HIV acquisition and that risk may increase with increasing numbers of concurrent HPV infections, and HPV infection clearance. Most HPV infections and lesions caused by HPV are transient and rarely progress to cancer.[24] The rarity of the development of persistent low-grade lesions, high-grade precancerous lesions, and cancer is mainly due to an effective immune response that includes recruitment of CD4 cells,[25–27] stimulation of cytokines,[27,28] which potentially also increases susceptibility to HIV infection, HIV transcription, and replication. Altogether, the immune response that leads to resolution of HPV infections and related precancerous lesions may, at the same time, facilitate HIV acquisition.

HPV VACCINATION

While HIV vaccines are likely many years away, 2 HPV vaccines are now licensed that have shown robust efficacy in females and males (>90%) against infection with the HPV types that are included in the vaccines, associated epithelial lesions, and anogenital cancers.[29–31] One prevents infection with 2 oncogenic HPV types (Cervarix) and the second prevents infection with 2 oncogenic HPV types as well as 2 nononcogenic HPV types (Gardasil). Trials of multivalent vaccines that incorporate virus-like particles of additional HPV types are currently underway. There are good reasons to implement HPV vaccination in sub-Saharan Africa, as cervical cancer is the leading female cancer in Africa.[32] However, due to logistical and financial reasons, the implementation of HPV vaccination in sub-Saharan Africa is lagging. If HPV vaccination could help prevent HIV infection, as well as HPV infection and its sequelae, the case for introduction of HPV vaccines in sub-Saharan Africa would be strengthened.

THE CASE FOR RANDOMIZED CLINICAL TRIALS

An inherent problem in observational studies including those reviewed previously is that HPV and HIV infection may be associated for reasons other than a biologic interaction between the 2 viruses. For example, sexual behavior is implicated in both infections. In studies where robust efforts are made to adjust for sexual behavior, residual confounding by

sexual behavior is still possible. Therefore, even high-quality longitudinal observational studies may not provide the definitive answer to the intriguing question of whether HPV infection predisposes a person to acquire HIV. A masked randomized controlled prevention trial of an HPV vaccine intervention could address this question, and, if the question is answered positively, would lead to another validated approach for HIV prevention in addition to circumcision, condom use, and possibly antiretroviral microbicide use. Notably, this would be an intervention that is technically simple to deliver, and after the 3-dose vaccination series is completed, poses no issues with adherence. In view of the proposed pathogenesis, a trial with a vaccine including more HPV types than the current vaccines, would be expected to have a greater impact than bi- or quadrivalent vaccines, and would be preferable.

ETHICAL ISSUES

Currently, one of the 2 HPV vaccines is licensed for men. However, since no country has included male vaccination in routine immunization programs, it cannot be regarded as a standard of care. Therefore, a placebo controlled trial of HPV vaccination among males is ethically justified.

Many countries have now included an HPV vaccine in their standard vaccination program for females. As HPV vaccines are preventive, not therapeutic, adolescents in the age range 11 to 13 years are the recommended group for vaccine dissemination. In several wealthier countries, short duration "catch-up" vaccination strategies among older adolescent girls (e.g., the Netherlands) or young women (e.g., Australia) are being conducted. However, countries with the highest incidence of cervical cancer, and therefore the greatest need for the vaccine, have not yet adopted national HPV vaccination strategies. Low-income countries have an opportunity in the future to develop national programs through Global Alliance for Vaccines and Immunisation programs once funding for this vaccine becomes available. However, several countries with a high incidence of both HIV and cervical cancer that are not Global Alliance for Vaccines and Immunisation eligible, such as South Africa, have not yet adopted national HPV vaccination programs, presumably for logistical or financial reasons. In the setting of less developed countries, it is unlikely that resources would allow for catch-up vaccination strategies, restricting vaccine dissemination to 11- to 13-year-olds instead. In countries where neither HPV vaccination nor cytologic screening to prevent cervical cancer are routinely offered, a randomized controlled trial among young women could be ethically conducted, provided participants are offered cervical screening services, information (and tools) of standard HIV prevention technologies (like condoms), contraceptives (the best way to prevent mother-to-child transmission of HIV), and HPV vaccination immediately after completion of the trial.

CONCLUSION

In conclusion, STIs increase the risk of HIV acquisition, and recent observational studies suggest that HPV may also have this effect. As it is very difficult to control fully for sexual behavior in observational studies, randomized controlled trials are needed to demonstrate whether HPV infections increase the risk for incident HIV. Such trials may offer a new tool for HIV prevention. Therefore, we propose that clinical trials be conducted that will test the utility of HPV vaccines as an intervention for the prevention of HIV infection.

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