HPV and HIV
Disease, infection and vaccination

Fondation Mérieux Conference Center
“Les Pensieres”
Veyrier du Lac - France

October 19-21, 2008

Scientific Committee:

• Catherine DUTEL
• Jean-Louis EXCLER
• Randy HYER
• Bernard IVANOFF
• Christophe LONGUET
• Benoit MIRIBEL
• Emilio LEDESMA

This meeting was made possible through unrestricted educational grants from Merck & Co, Inc.
Welcome Letter

October 19, 2008

Dear Participant,

It is our pleasure to welcome you to the symposium entitled: ‘HPV and HIV - Disease, infection and vaccination’ in Fondation Mérieux’s Conference Center “Les Pensières.” We hope you will enjoy this meeting, which brings together some of the world’s foremost experts. The format of the discussion is intended to generate discussion and interaction among participants and to foster the dissemination of new information on this topic. The conference will provide an opportunity for specialists to exchange their knowledge and experience through collaboration with researchers from around the world.

Over the next three days, the team at Les Pensières will be on hand to help you with any question you may have and to make your stay and conference as comfortable and valuable as possible.

Benoît Miribel
Directeur Général
Fondation Mérieux

For more information: www.fondation-merieux.org

Background and rationale

The understanding of HPV and HIV transmission, disease manifestations, and the role of vaccination is rapidly evolving. With the recent introduction of the HPV vaccine, the global scientific and public health communities have a potent motivation to even better understand these relationships. The HPV vaccine offers tremendous benefit to women and potentially men in reducing HPV disease. Regarding HIV, there remain important questions regarding the HPV vaccine to include: what is the likely benefit to HIV positive individuals, are we able to vaccinate HIV infected individuals, and among HIV uninfected individuals would HPV vaccination help reduce transmission of HIV?

It is established that HIV disease affects the frequency, virulence, and time-course of HPV diseases. HIV positive women with HPV cervical disease progress more rapidly to invasive cervical cancer than those HIV negative. Likewise, genital wart disease is extensive and unremitting in women (and men) with HIV mediated immuno-suppression. HPV is also considered to be more easily transmitted from those with HIV infection or disease. HPV vaccination of HIV positive individuals does seem feasible and could protect those who are still susceptible to the vaccine types. There are data now in the public domain showing that HPV vaccination induces seroconversion in HIV infected children and other studies in adult men and women with HIV infection are underway.

In regard to HIV transmission, it is known that ulcerative genital disease facilitates the transmission, i.e., individuals with diseases like syphilis and genital herpes diseases are at increased risk for HIV acquisition. Epidemiological studies, though cross-sectional, point to a strong link between genital warts and HIV infection. Enhanced friability and inflammation of the cervix from HPV disease or infection could increase susceptibility to HIV infection in a manner similar to other genital infection. It has been shown that HPV anal infection confers risk of HIV acquisition in a prospective, though limited, study. These facts, thus, pose an interesting question: if HPV infection or disease (including genital warts) does increase susceptibility to HIV infection, would HPV vaccination help protect against HIV infection?

Given the proven benefit of HPV vaccination to women (and likely men) and the great public health need to control HIV, what are the key questions regarding HPV vaccination to prevent HIV infection? These likely include: is it necessary to confirm or quantify the relationship between HPV disease and HIV transmission for cervical disease and genital warts? Would clinical efficacy against HIV transmission be possible? If so, how? What is needed to help us understand HPV vaccines on HIV transmission, given the ubiquity of HPV infection? What level of evidence is needed for policy recommendations? This scientific symposium on HPV and HIV will attempt to address the above questions and suggest future basic, clinical, and public health related research.

The Conference’s strategic objectives include:

- To better the scientific understanding, disseminate knowledge, and debate critical questions regarding the interactions and relationships between HPV and HIV infections, diseases, and vaccines
- To foster dialogue and scientific exchange among different actors of the scientific and policy communities involved in vaccinology
- To focus the discussions on research to obtain the best use of vaccination against these two infections.
### Scientific Program

**Sunday October 19, 2008**

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**Monday October 20, 2008**

**Session 1.a**  
**The effect of HIV on HPV disease**  
*Chaired by Mike Cohen*

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**Session 1.b**  
**STIs and transmission of HIV**  
*Chaired by Sebastian Videla*

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**Session 2**  
**Update on HPV and HIV vaccines**  
*Chaired by Stewart Massad and Patti Gravitt*

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Session 3
Would HPV vaccination reduce the risk of HIV infection?
Chaired by Norbert Brockmeyer and Marian Neutra

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HPV anal infection/disease as a risk of factor for HIV acquisition
Peter CHIN HONG

08h50 - 09h10
Discussion

09h10 - 09h30
Prospective epidemiological studies of HIV and HPV
Frank TAULO

09h30 - 09h50
Discussion

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Coffee Break

10h20 - 10h40
Biological and immunological basis of HPV vaccination reducing HIV transmission
Darron BROWN

10h40 - 11h00
Discussion

11h00 - 11h20
Evidence from other preventive intervention: education, circumcision, treatment of STIs
Connie CELUM

11h20 - 11h40
Discussion

12h00 - 14h00
Lunch

Session 4
Future research on HPV/HIV interaction
Chaired by Helen REES

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Basic research: serological and cellular criteria for assessing potential impact - VLP’s approach
Charlotte DALBA

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Clinical research: are efficacy trials feasible? What epidemiological studies are needed?
Laura KOUTSKY

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Public health: what would be needed to recommend HPV vaccination to help prevent HIV infection?
Deborah MONEY

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Discussion

16h00 - 16h30
Conclusion

16h30
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The effect of HIV on HPV disease

Benign and malignant HPV-associated diseases in HIV-positive men

Alexander KREUTER
Department of Dermatology - Ruhr University Bochum - Germany

Human papillomavirus (HPV) infections belong to the most common sexually transmitted infections worldwide. While most HPV-infections in the general population are eliminated over time, HPV-infections often persist in immunosuppressed individuals.

In HIV-infected men who have sex with men (MSM), anal HPV prevalence is more than 90% and infections with multiple HPV types are common. HPV-associated anogenital malignancies occur with high frequency in these patients. Anal intraepithelial neoplasia (AIN), a potential precursor lesion of squamous cell carcinoma of the anus, is causally linked to persistent infections with high-risk HPV.

To date, only limited data is available on the incidence and prevalence of HPV infections at other locations (oral cavity and penis) in HIV-positive MSM.

In our own cohort in Bochum (n = 263), 44% of all patients presented with penile HPV-infection and 22% had oral HPV infection (mostly HPV16). 4.2% of all patients presented with penile intraepithelial neoplasia (PIN), whereas 59% had AIN of any grade. Penile condyloma were present in 15% and anal condyloma were present in 57% of all patients, respectively. These findings indicate that all HIV positive MSM should be regularly screened for PIN and genital condylomata acuminate in addition to AIN screening.
Epidemiology of HPV infections in HIV-positive individuals

Silvia FRANCESCHI
International Agency for Research on Cancer - Lyon - France

Although early studies on the association between HIV and invasive cervical cancer showed somewhat inconsistent findings [IARC, 1995; International Collaboration on HIV and Cancer, 2000], it has become increasingly clear that HIV-positive women are also at increased risk of invasive cervical cancer [Franceschi et al., 1998; Frisch et al., 2000]. The relative risk of invasive cervical cancer among HIV-positive women, however, varies from one country to another, and depends largely on competing causes of premature death (e.g., in sub-Saharan Africa) [Sitas et al., 2000; Mbulaiteye et al., 2006] or prevention of the progression of pre-invasive lesions as a result of early detection in screening programs (e.g., the United States) [Frisch et al., 2000]. Indeed, HIV also unfavourably affects the natural history of human papillomavirus (HPV) infection. The clearance of HPV infection is diminished among immunocompromised individuals, and reactivation and progression to neoplastic lesions become more probable [Moscicki, 1999; Strickler et al., 2003].

Several studies have found a broader range of both high- and low-risk HPV types in HIV-positive compared with HIV-negative women [Ellerbrock et al., 2000; Goncalves et al., 1999; Palefsky et al., 1999]. In a recent meta-analysis on 20 studies including 5,578 women with HIV worldwide, HPV16 accounted for a smaller proportion of HPV infections in HIV-positive women than in the general female population. This was also the case in women with high-grade squamous intraepithelial lesions (HSIL) [Clifford et al., 2006]. Conversely, other types (high-risk types 18, 51, 52, 58 and low-risk types 11, 53, 61) were more frequently detected in HIV-positive women with HSIL. The HIV Epidemiology Research Study showed that HPV16 was more weakly associated with immune status than the other HPV types (i.e., the control of HPV16 is also a challenge for immunocompetent women) [Strickler et al., 2003]. In addition, HIV-positive women with or without cervical lesions also harbour more multiple-type HPV infections, compared with the general female population [Clifford et al., 2006].
Ulcerative and non-ulcerative genital lesions and HIV acquisition

Myron S. Cohen
University of North Carolina - Chapel Hill - USA

Transmission of HIV-1 depends on infectiousness of the “index case” and susceptibility of those who are uninfected. Overwhelming epidemiological and ecologic data demonstrate that STDs amplify the probability of HIV transmission, and there are several credible mechanistic explanations for such observations. These explanations include the fact(s) that i) STDs can increase HIV genital tract viral burden; ii) HIV can increase viral diversity; iii) STDs can disrupt tissue barriers and defenses; iv) STDs increase the number of cells receptive to HIV and the number of receptors/cell. In addition, in vitro and pathogenesis experiments provide more detailed biologic plausibility for the effects of STDs, either thru direct interactions or specific cytokines. Paradoxically, it has been difficult to demonstrate that population level treatment of STDs can effect HIV incidence, suggesting that the interventions available are not properly directed or sufficient. From a practical point of view, all STDs (including HIV) “live in the same neighborhood” and the study of HIV transmission (and prevention of transmission) must always consider the effects of STD cofactors.

Interactions between HPV and HIV: STIs and HIV shedding, regulation of HPV by HIV, and HPV VLP influence upon HIV

Jennifer Smith
University of North Carolina - Chapel Hill - USA

Several studies among HIV-seropositive women have shown increased HIV shedding associated with genital ulcers or co-infection with other sexually transmitted infections. In contrast, relatively few published studies have examined associations between HPV infection, cervical neoplasia, and HIV shedding. Two studies found higher HIV RNA shedding among HIV-seropositive women infected with HPV infection compared to those HPV uninfected, while a third study found no difference. Albeit limited to relatively small sample sizes, two studies found that HIV-seropositive women with cervical lesions, including high-grade squamous intraepithelial neoplasia (HSIL), had greater HIV viral shedding, as compared with women without cervical abnormalities.

Limited data are also available on whether HPV infection or cervical neoplasia is associated with an increased risk of HIV acquisition. Among women, only one published abstract is available. A randomized controlled trial (RCT) among 2,040 HIV-seronegative women in Zimbabwe found a higher risk of HIV seroconversion among women who are HPV DNA at baseline, in comparison to those HPV negative at the baseline visit for any HPV type (OR=1.6, p=0.04). Similar results have been noted among HIV-risk men. There are no data, to our knowledge, that report the influence of HPV persistence over time, or of clinically ascertained cervical neoplasia, on the risk of HIV acquisition.

In terms of regulation of HPV by HIV, the HIV Tat protein appears to play a role in modulating HPV gene expression. Higher HIV Tat levels have been shown to correlate with higher HPV E7 levels in biopsies of condylomas of HIV-seropositive individuals. HIV Tat also appears to have an effect on HPV gene expression in cervical carcinoma cells co-cultivated with HIV-1 infected cells. Following HIV-1 Tat addition to the culture, HPV18 infected epithelial cells were found to have increased HPV18 E1 and L1 RNA levels in a dose dependent manner. These findings suggest that HIV-1 may promote HPV-associated cervical carcinogenesis. Whether HIV infects cervical epithelial cells is currently debated. Thus, in vitro cell cycle regulation by HIV may not apply in vivo if HPV-infected epithelial cells may not be infected by HIV.
Suite

The number of Langerhans cells in cervical specimens has been shown to be significantly lower in women with detectable HIV viral loads compared to those with undetectable HIV viral loads or HIV-seronegative. Such an HIV-mediated decrease in cervical Langerhans cells could impair local immune responses to HPV infection.

Two recent studies have reported that the HPV-virus like particle (VLP) may induce the expression of anti-HIV-1 cytokines. One study of the effect of the HPV-16 L1 VLP on HIV-1 replication found that the HPV-VLP may strongly inhibit HIV viral replication in CD8-negative peripheral blood mononuclear cells (PBMCs) and monocyte-derived macrophages (MDMs) without affecting CD4, CCR5, and CXCR expression. This study also found that the HPV-16 L1 VLP may induce the production of a novel antiviral cytokine IL-27 that may act as a strong inhibitor of HIV-1 replication in PBMCs, macrophages, and CD4+ cells.

Session 2:

Update on HPV and HIV vaccines
An update of the GARDASIL® (Quadrivalent Human Papillomavirus [HPV] Vaccine) Clinical Trial Program

Randall N. HYER
Merck Vaccines and Infectious Diseases - USA

Introduction: In 2006, GARDASIL® was licensed in the U.S. and Europe. Licensure was primarily based on a 2-year demonstration that GARDASIL® prevented HPV16/18-related high-grade precancerous lesions (CIN2/3 and AIS). Due to the high efficacy seen in FUTURE I-II, the independent Data and Safety Monitoring Board recommended vaccination of women in the placebo group earlier than planned. Here we present end-of-study data of the efficacy of GARDASIL®. We also present data in women aged 24-45, prevention of reinfection, and describe an ongoing study in men.

Results: Among women aged 16-26 who remained naïve to HPV6/11/16 or 18 through completion of the 3-dose regimen, vaccine efficacy for HPV16/18-related CIN2/3 or AIS was 98% (95%CI: 94-100). Efficacy for HPV6/11/16/18-related condyloma, VIN1-3, and VaIN1-3 was 99%, 100% and 100%, respectively. Among women aged 24-45, vaccine efficacy for any HPV6/11/16/18-related disease was 92% (95%CI: 50-100).

No subject receiving GARDASIL® developed disease due to a vaccine-HPV-type to which they were seropositive and DNA negative at enrollment. In this cohort of previously infected women, vaccine efficacy was 100% for CIN1 or worse (95%CI: 29-100) and condyloma/VIN1-3/VaIN1-3 (95%CI: 40-100). These results suggest that infection-elicited antibodies may not provide complete protection over time, and that GARDASIL® may prevent recurrence or reactivation of disease.

Protocol 020 was designed to evaluate efficacy in men (~3 years duration). We enrolled heterosexual men aged 16-23 and men who have sex with men (MSM) aged 16-26 with <5 lifetime sex partners. The primary efficacy objective is to demonstrate that GARDASIL® reduces the incidence of HPV6/11/16/18-related genital warts, penile/perianal/perineal intraepithelial neoplasia and cancer. In MSM, an additional objective is to investigate the impact of GARDASIL® on the incidence of HPV6/11/16/18-related anal intraepithelial lesions or cancer.

Discussion: Vaccination with GARDASIL® is expected to greatly reduce the burden of cervical and other cancers, dysplasia, and genital warts.

Abstract submitted and accepted by the Vaccine Congress, 2008.
Interim results of the Phase III trial (PATRICIA trial, n=18,644 women, aged 15–25 years) showed 100% vaccine efficacy against HPV16/18 associated CIN2+, based on an additional causality analysis. Evidence of cross-protection against persistent infection caused by HPV-45, -31 was also shown. Cervarix™ demonstrated high and sustained immunogenicity (total IgG and neutralizing antibodies) against both HPV-16 and -18, with >98% seropositivity up to 6.4 years of follow up in women 15-25 years.

Clinical trials in girls 10–14 and women 15–55 have shown that the vaccine is highly immunogenic across the age range 10-55 years. Evaluation of the immune response at the site of infection has shown a high correlation between the concentration of anti-HPV-16 and -18 antibody titers measured in serum and in cervico-vaginal secretions (CVS).

In addition, based on mathematical modelling, vaccination with Cervarix™ is predicted to provide sustained antibody levels for both HPV-16 and -18 for at least 20 years.

Long-lasting protection will be particularly beneficial in case of routine vaccination of (pre-)adolescent girls, as the need for boosters will have significant public health impact. It remains currently unproven that recall of vaccine-induced immune memory by natural infection is present or sufficient for long-term protection. High and sustained levels of neutralizing antibodies may be predictive of the vaccine’s preventive potential in the future.

Cervarix™ is a trade mark of the GlaxoSmithKline group of companies.

References:

Challenges and Prospects for AIDS Vaccines

Jean-Louis EXCLER
IAVI - Geneva - Switzerland

Now well into the third decade of the pandemic of human immunodeficiency virus (HIV) and AIDS, we have seen dramatic successes in the treatment of HIV-infected persons in many countries. Yet the pandemic still rages, with 2.7 million new infections in 2007, the heaviest burden being in developing countries. Indeed, for every infected person who began receiving antiretroviral therapy in 2007, 2.5 people were newly infected with HIV. Although the search for an HIV vaccine remains among the highest public health priorities, the identification of a preventive HIV vaccine has thus far eluded the biomedical research community, mainly because of the significant scientific obstacles presented by the virus.

Over the past 20 years, the empirical approach to HIV vaccine focusing on inducing neutralizing antibodies to primary isolates with different envelop constructs or inducing T-cell responses using vector-based vaccines has failed so far. The Merck Ad5 HIV-1 candidate vaccine advanced to a phase 2b test-of-concept trial known as STEP, neither prevented infection nor had an impact on early plasma virus levels in those who received the vaccine compared with the placebo recipients. In addition, there was an unexpected trend toward a greater number of vaccine recipients infected, compared with the placebo recipients, in particular in uncircumcised men. A Phase III trial with a pox vector prime and gp120 boost in on going in Thailand for definitive results expected in August 2009.

These results have deeply shaken the scientific community to reconsider entirely their approaches. Major efforts are now conducted to design immunogens inducing broadly neutralizing antibodies against HIV-1 primary isolates. Similarly, designing immunogens and vector-based strategies inducing broad and sustained T-cell responses able to contain virus replication as well as the live-attenuated SIV are underway. The need to broaden research directed at answering fundamental questions in HIV vaccine discovery through laboratory, nonhuman primate (NHP), and clinical research has recently been emphasized. New clinical trial designs are needed such as a Screening Test-of-Concept Trials (STOC) to accelerate development.

This worldwide effort needs sustained political, financial and community support, recruitment and retention of young researchers in particular in developing countries, for the next 20 years.
Immunogenicity of HPV Vaccine in HIV Positive Individuals

Alfred J. SAAH
Merck Research Laboratories - USA

Merck Research Laboratories and IMPAACT partnered to perform an immunogenicity and safety study, Protocol 1047, in approximately 130 HIV-infected children aged 7 to 12 years. The results were presented at the CROI, 2008 in Boston, MA, Poster 619a by Dr. Adriana Weinberg and the P1047 team.

Children were stratified by the following characteristics:
A: CD4% Nadir < 15 and CD4% ≥15 at screening
B: CD4% Nadir > 15 and < 25 and CD4% ≥ 15 at screening
C: CD4% Nadir ≥ 25 and CD4% ≥ 25 at screening

Adverse events were assessed at clinic visits and by telephone follow-up after each dose of the vaccine. CD4 and plasma HIV RNA were measured at entry and after each immunization. HPV-specific immune responses were assessed at entry and week 28. The study showed that the quadrivalent HPV vaccine was highly immunogenic and was generally safe and well tolerated. Seroconversion to all HPV types occurred in greater than 99.5% of study participants irrespective of HIV disease stratum.

Additionally, Merck is collaborating with other groups in the HIV/AIDS research community: the AIDS Malignancy Consortium (AMC) is performing a pilot study in approximately 100 HIV-infected men, and the AIDS Clinical Trials Group (ACTG) is performing a safety and immunogenicity study of 400 women with HIV-infection. Others studies are being supported through the Merck Investigator Studies Program, which supports investigator-initiated research.
Session 3:

Would HPV vaccination reduce the risk of HIV infection?

Objective:
Human papillomavirus (HPV) is a common sexually transmitted agent that causes anogenital cancer and precancer lesions that have an inflammatory infiltrate, may be friable and bleed. This paper will discuss the association between anal HPV infection and HIV acquisition.

Methods:
In one prospective cohort study we recruited 1409 HIV-negative men who have sex with men from a community-based setting in Boston, Denver, New York and San Francisco. We used Cox proportional hazards regression modeling and assessed the independent association of HPV infection with the rate of acquisition of HIV infection.

Results:
Of 1409 participants contributing 4375 person-years of follow-up, 51 HIV-seroconverted. The median number of HPV types in HPV-infected HIV-seroconverters was 2 (IQR, 1-3) at the time of HIV seroconversion. After adjustment for sexual activity, substance use, occurrence of other sexually transmitted infections and demographic variables, there was evidence (P<0.05) for the effect of infection with ≥2 HPV types (HR 2.5, 95% CI 1.02-6.3) in HIV seroconversion.

Conclusion:
Anal HPV infection is independently associated with HIV acquisition. Studies that incorporate high-resolution anoscopy to more accurately identify HPV-associated disease are needed to determine the relationship between HPV-associated disease and HIV seroconversion.
Prospective epidemiological studies of HIV and HPV

Frank TAULO
Centre for Reproductive Health - Blantyre - Malawi

Background:
Human Papilloma Virus (HPV) has firmly been established biologically and epidemiologically as a cause of cervical cancer. Though HPV is the agent but it is not sufficient on its own. There are other factors which attribute to the cause and progression of disease i.e. cofactors. Some of these cofactors include hormonal contraceptives, high parity, tobacco smoking, co-infection with Chlamydia trachomatis, herpes simplex, immunosuppression and certain dietary deficiencies. With the advent of HIV/AIDS, co-infection with HIV has also been identified as a co-factor. This review will address this linkage, thus HPV/HIV and cervical cancer.

Goal:
To summarize recently published epidemiological findings that assist the understanding of the natural history of cervical and HPV infection and cervical cancer among HIV infected individuals.

Results/Findings:
HIV infection and associated immunodeficiency are known to alter the cause of HPV. Some studies have shown that HIV infection may strengthen the effect of HPV at cervical level. Moreover, the increased frequency and severity of cervical diseases among women with HIV infection has raised the issue of whether HIV and HPV play a pathogenetic role and what their relationship to one another is. It is postulated that the viral pathogenetic effect is probably mediated through the HIV-induced immunosuppression. Several hypotheses have been postulated which are conflictual.

It has been suggested that HIV-induced immunosuppression either increases the capacity of HPV to infect the epithelial cells of the cervix or it has an effect on HPV replication, as suggested by the higher prevalence of cervical lesions. Another thinking has postulated a molecular interaction between HIV/HPV, though not well defined. It has been suggested that in HIV infected women, there is an upregulation of HPV E6 and E7 genes expression by HIV proteins (TAT).

Conclusion:
Although the precise biological mechanism underlying the interaction between HIV and HPV has yet to be determined, there are two potential mechanisms for the interaction. The first one is the HIV and its resultant effects on immune function affect the susceptibility to, severity of, and/or potential oncogenicity of HPV. The second one is at a molecular interaction level between HIV and HPV.

Biological and immunological basis of HPV vaccination reducing HIV transmission

Darron BROWN
Indianapolis School of Medicine - USA

More than 50% of newly acquired HIV infections occur in women, most of whom are infected by heterosexual exposure. The exact mechanisms involved in sexual transmission of HIV are not completely understood. Both HPV infections and HPV-induced cancers may facilitate heterosexual transmission of HIV. Cervical infections with human papillomavirus (HPV) are extremely common in young women. The type-distribution of infections is broad, and HPV vaccine types (6, 11, 16, and 18) are not necessarily the most common types detected in young women. In contrast, HPV-induced cancers, occur in older women and are caused primarily by a select few HPV types such as HPV 16, which causes half of all cases.

How could HPV facilitate HIV transmission? First, HPV infection induces the recruitment of potential target cells for HIV infection such as CD4 cells and macrophages to the cervix. Second, HPV infection (and, of course HPV-induced cancer) stimulates angiogenesis, a process that may allow direct exposure of incoming HIV to blood.

Third, HPV infection induces local production of inflammatory cytokines (Il-6, TNF-alpha) that promote transcription and replication of HIV. Lastly, HPV-induced dysplastic lesions are easily detached from basement membranes, due to loss of hemidesmosomes, and the resulting friability of cervical tissue may promote HIV infection by sexual transmission. Are all genital HPV types created equally in inducing these four changes in the cervical environment? Unfortunately, we do not know.

If HPV infection facilitates HIV transmission, will HPV vaccines help reduce HIV transmission? To answer this question, several issues must be considered. First, do all HPV infections induce the changes mentioned above, or do only oncogenic HPV types, or more specifically, do only vaccine types (HPV 6, 11, 16, and 18) cause these changes? Second, in a population of young, sexually active women, of the 60 to 80% who will be infected with HPV, what percentage will be infected with vaccine types? It must be kept in mind that while HPV 16 and 18 together cause ~70% of cervical cancers, these types cause only about 15% of all cervical infections in young women.
Therefore, if cervical HPV infection with any HPV type(s) is indeed a risk factor for sexual transmission of HIV, then one could make several predictions. First, while the current HPV vaccines prevent infection and disease due to vaccine types (with a moderate degree of cross-protection), many other non-vaccine type HPV infections occur in young women, and therefore HPV vaccines would not reduce HIV transmission in these women. Second, multiple-type HPV infections are very common, and even though infection and disease with the major cancer-causing HPV types (16 and 18) are prevented, many other types will not be prevented. Even though these frequently detected, non-vaccine HPV types cause less disease than HPV types 6, 11, 16, and 18, they may contribute to the immunologic and vascular changes mentioned above that are potential facilitators of HIV transmission. Obviously, further studies are needed, and perhaps the availability of multivalent HPV vaccines as well.

Evidence from other preventive interventions: education, circumcision, treatment of STIs

Connie CELUM
University of Washington - Seattle - USA

Methods:
Four randomized trials of male circumcision among HIV-negative and HIV-positive men were conducted in Africa and 2 randomized placebo-controlled trials of HSV-2 suppression (acyclovir 400 mg bid) were conducted among HIV-negative HSV-2 seropositive African women and gay men from Latin America and the US. A multi-center, randomized placebo-controlled trial of HSV-2 suppression (acyclovir 400 mg bid) among African HIV serodiscordant couples in which the HIV+ partner is HSV-2 seropositive and has CD4>250, not on ART, is ongoing and will evaluate efficacy of HSV-2 suppression on HIV transmission and disease progression. A second trial of HSV-2 suppression on HIV disease progression is ongoing in Rakai. Multiple community-level and individual randomized trials of STI control and education have been conducted in Africa.
Results:
The 3 randomized trials of male circumcision in HIV- men showed a reduction in HIV acquisition of 50-60% and some of the trials showed reductions in HSV-2 seroincidence, GUD incidence, HPV, and vaginal infections. The trial of male circumcision among 171 HIV+ men in HIV discordant couples resulted in a RR of 1.59 (95% CI 0.7-1.4), and increased risk (RR 2.9, p=0.06) among couples who resumed sex before wound healing. Two HSV-2 suppression trials in HIV-negative, HSV-2 seropositive persons showed no reduction in HIV acquisition inspite of a significant reduction in genital ulcers overall and 64% reduction in HSV-2 DNA PCR+ genital ulcers in the acyclovir arm of the multi-center HPTN 039 trial. The trials of HSV-2 suppression in HIV/HSV-2 co-infected persons are ongoing. Trials of STI control (primarily syndromic management) and education about risk behaviors have generally not reduced HIV incidence, except in nascent epidemics such as in Mwanza Tanzania in the early 1990s.

Conclusions:
Male circumcision has been demonstrated to reduce HIV incidence among African men, and to reduce incidence of GUD and HPV among men and vaginal infections among their female partners. Circumcision of HIV+ men has not been demonstrated to reduce HIV transmission to female partners, in part due to early resumption of sex, indicating the need for counseling about wound healing. HSV-2 suppression with acyclovir 400 mg bid did not reduce HIV acquisition among African women and gay men in the Americas. Results are awaited of the ongoing trials of HSV-2 suppression on HIV transmission and disease progression among HIV/HSV-2 co-infected persons, for which there is biologic plausibility and pilot data indicating reductions in plasma and genital HIV levels. Most trials of STI control and education have not reduced HIV incidence.

Whereas male circumcision is an exciting new HIV prevention intervention for HIV-negative men, STI control and HSV-2 suppression have not been shown to reduce HIV incidence. Additional biomedical HIV prevention strategies are needed, as well as combination prevention strategies of partially effective behavioral and biomedical interventions.

Session 4:
Future research on HPV/HIV interaction
Basic research: serological and cellular criteria for assessing potential impact - VLP’s approach

Charlotte DALBA
Epixis - Paris - France

Retrovirus based virus-like particles (Retro-VLPs) represent a useful and flexible technology that can be used both as a versatile platform for vaccines and immunotherapeutics and as a base for neutralizing antibody assays. The Retro-VLPs are applicable to a wide range of viruses, including but not restricted to HIV and HPV, and the assays can be performed in low containment laboratories with low biosafety levels.
Public health: what would be needed to recommend HPV vaccination to help prevent HIV infection?

Deborah MONEY
Women’s Health Research Institut - Canada

This talk will consider data on the HPV vaccine and its relevance to HIV infection that may inform potential public health decisions on implementation for the purpose of preventing HIV disease.

In order to consider a vaccine for implementation in a public health/population based setting, the Erickson, De Wals, Farand* framework will be presented as a potentially useful methodology on which to evaluate a new vaccine for public health. Insertion of the evidence to date into a set of criteria in 13 categories may permit an objective evaluation of the status of the HPV vaccine for this purpose.

The categories for consideration are: burden of HIV disease (specific to the region or population in question); characteristics of the HPV vaccine; immunization strategies; cost effectiveness (for prevention of HIV disease); acceptability (to individuals, the public, governments etc.); feasibility (e.g. ability to time with other vaccines); ability to evaluate (e.g. ability to assess rates/changes in HIV acquisition in population in which vaccination is to be implemented); research questions (e.g. at what point can a vaccine be implemented with research questions such as duration of protection not yet answered); equity; ethical; legal; conformity of programs; political.

It is proposed that key gaps in data for this framework will inform what future research is needed. Public health requires sufficient information on the utility of the HPV vaccine to prevent HIV infection prior to consideration of implementation for this purpose beyond prevention of strictly HPV related diseases.

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