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Human Papillomavirus Vaccination in HIV-infected Women: Need for Increased Coverage

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Abstract

HIV-infected women carry a significant burden on HPV infection and associated diseases. As HIV-infected individuals are living longer, the prevalence of HPV infection is rising and HPV-associated cytologic abnormalities remain high despite successful treatments of HIV infection. Several HPV vaccines are currently available and recommended for adolescents and adults up to age 26. The vaccine is safe, immunogenic and effective in preventing diseases due to HPV types included in the vaccines, particularly among persons without prior HPV exposure. This review summarizes available data on the use of the HPV vaccines among HIV infected women. The immunogenicity and safety of the vaccine is highlighted and in particular, barriers to vaccination among HIV infected women are discussed.

Introduction

Human papillonaviruses (HPV) are non-enveloped double-stranded DNA viruses in the Papillomaviridae family. HPVs have a circular genome enclosed in a capsid shell which is made of major and minor capsid proteins L1 and L2 respectively. Over 170 types have been identified [1] and of these, 40 types are sexually transmitted during anal, vaginal and oral sex and infect the anogenital area of both men and women [2]. The lifetime risk for HPV infection among sexually active men and women is at least 50%, and by 50 years of age, 80% of women will have acquired HPV infection (REF CDC). Most HPV infections are transient, it is not clear if the virus is fully cleared by the host or if it is maintained in a latent phase in the epithelium [3].

Persistence of high-risk types of HPV (16, 18, 31, 33, 35, 45 are most prevalent) causes squamous dysplasia and cancer. Worldwide, types 16 and 18 account for the majority of cervical cancers [4], and one or more of these types can be found in 90% of high grade intraepithelial precursor lesions and almost all cervical cancers [5, 6]. In addition, oncogenic HPV cause 40-90% of anal, vulvar, vaginal, penile and oropharyngeal cancers [7, 8]. Non-oncogenic types 6 and 11 are the etiologic agents for the majority of genital warts. Of the estimated 12.7 million new cancers occurring in 2008 worldwide, almost 5% were attributable to HPV infection [7].

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HPV and HIV Co-infection

HIV-infected individuals are living longer, and non-AIDS-defining conditions are affecting this population in increasing numbers. HPV infections are more prevalent and persistent in HIV-infected women and men. Earlier studies reported anal HPV prevalence rates of 76% in HIV-infected women and 46% in HIV-uninfected women and cervical prevalence rates of 48% to 73% compared to 28% in HIV-uninfected women [9-12]. Despite the immunologic reconstitution associated with the use of combination antiretroviral therapy (cART), the prevalence of anogenital HPV infections and diseases remains high [13-16]. In a recent contemporary cohort of HIV-infected women receiving effective antiretroviral therapy (SUN study, Study to Understand the Natural History of HIV), anal and cervical HPV infections were highly prevalent, with anal HPV prevalence rates of 90% and cervical rates of 83% [17]. The higher prevalences observed are due in part to improvements in PCR methodology that have occurred since these earlier studies were performed; the Linear Array (LA) assay detects 37 high- and low-risk HPV types compared with earlier assays that captured 7 to 29 types . It is noteworthy that the prevalence of anal HPV infection is greater than the prevalence of cervical HPV infection in HIV-infected women, a fact also noted in other studies. In the Women's Interagency HIV Study, prevalent HPV infection rates in the anus and cervix among 251 women were 79% and 53%, respectively [12]. Similar results were found in a smaller study of 114 women; prevalent anal HPV infection was twice as frequent as cervical HPV infection (67% vs. 34%) [18]. Among, HIV-infected women, lower CD4 cell count is associated with greater risk of concomitant oncogenic and non-oncogenic HPV infections [19]. Anogenital HPV infection is multicentric and anal HPV infection may be a reservoir and cause cervical infection and vice versa.

With rising HPV prevalence rates among HIV-infected individuals, it is not surprising that HPV-associated cytologic abnormalities and cancers remains high. Co-infection with HIV and HPV increases the risk for HPV-associated cancers, likely either due to HIV-induced immune dysfunction or factors related to HPV, such as longer persistence and increased replication of HPV[13, 19, 20].

Cervical cancers remain high in the cART era among HIV-infected women [21]. In a study from cancer registries in the USA, invasive cervical cancer (ICC) risk was significantly increased (standardized incidence ratio 2.9) compared with the general population [22]. Nevertheless, among HIV-infected women who received regular screening and recommended follow-up treatment, after a median follow-up of 10.3 years, the incidence of ICC was not higher (21.4 of 100 000 person-years) compared with HIV-negative women (0 of 100 000 person-years; $P = 0.59$), suggesting a positive impact of screening in the HIV-infected population similar to the impact seen in the general population [23].

Similarly, the incidence of anal cancers is increasing in HIV-infected persons in the cART era. In a large analysis of cancer incidence trends among HIV-infected persons in the United States from 1992 to 2003, both the incidence of anal cancer and the relative incidence of anal cancer in HIV-infected persons compared with the general population increased over time [15]. Data from the US AIDS cancer registry have also documented increasing incidence of anal neoplasia among HIV-infected women [24]. There does not appear to be

concordance between cytologic abnormalities in the anus and cervix. In the SUN study, there was no difference in the prevalences of anal and cervical cytologic abnormalities and the presence and extent of disease at these anatomical sites were not concordant. The presence of cytologic abnormalities in the cervix was found to be an imperfect predictor for cytologic abnormalities in the anus [17]. In a multicenter longitudinal study of HIV-infected women in the US to assess concomitant anal and cervical HPV infections and intraepithelial neoplasia, similarly there was little correlation between severity of anal and cervical disease [19].

Immune response after natural HPV infection

Both humoral and cellular immune responses to natural HPV infection have been documented. Humoral response leads to the development of neutralizing antibodies against the viral L1 protein capsid that are useful in the prevention of primary infection of basal keratinocytes. After the HPV enters the cell, its clearance is dependent on cytotoxic T cells that react with infected cells through the recognition of expressed viral protein. Correlates of immunity have not been established.

Natural HPV infection induces a low level of antibody production that for most types does not seem to confer protection against subsequent type-specific HPV infection [3]. Viscidi et al. evaluated the prevalence of serum antibodies to HPV types 16, 18, 31, 35, and 45 in 829 HIV-infected and 413 HIV-uninfected risk- matched women enrolled in the HIV Epidemiologic Research (HER) study and analyzed the association of seropositivity with risk of detection of HPV DNA in the genital tract during follow-up . The seroprevalence of HPV 16 antibodies was 51.8% in HIV-infected women compared with 45.5% in HIV-uninfected women, and that of HPV 18 was 52.0% and 35.6% in HIV-infected and -uninfected women, respectively [25]. There was no statistically significant difference in the risk of a new infection with the homologous HPV type between HPV seropositive and HPV seronegative women. This was true for both HIV-infected and non-infected women for all types tested except for HPV 45. HIV-infected women who were HPV 45 seropositive had a lower risk of a new HPV 45 infection 4.5 years later [25]. This suggests that natural HPV infection does not confer immunoprotection for most HPV types.

Immune response after vaccination

The quadrivalent HPV vaccine Gardasil™ (Merck & Co., Inc.) (qHPV vaccine) was approved by the U.S. Food and Drug Administration (FDA) in June 2006 for use in females with the recommendation for routine vaccination at age 11 or 12 years and for those aged 13-26 years previously unvaccinated[26]. In 2009, the qHPV vaccine was licensed in males [27], with recommendations in late 2011 for routine vaccination of males age 11 or 12 and for those aged 13-21 not previously vaccinated [28]. The vaccine consists of virus-like particles (VLP) generated by the expression of the major capsid protein L1 from HPV types 6, 11, 16, and 18 with an aluminum adjuvant. The Advisory Committee on Immunization Practices (ACIP) recommends that the vaccine be routinely given to girls when they are 11 or 12 years of age, before people become sexually active (i.e., before they are exposed to the viruses). The bivalent HPV vaccine Cervarix™ (GlaxoSmithKline) (bHPV vaccine) was

approved by the U.S. Food and Drug Administration (FDA) in October 2009 for females aged 9 to 25 years. It is a L1 VLP vaccine that includes HPV types 16 and 18 with an adjuvant ASO4, which consists of alum combined with a TLR4 ligand (3-O-desacyl-4-monophosphoryl lipid A) [29]. Both vaccines are to be given as a 3-dose series completed over 6 months.

Both vaccines are recombinant vaccines produced by inserting the L1 gene into a host (yeast for the qHPV vaccine and baculorus for the bHPV vaccine) which then produces L1 proteins in high concentrations. The L1 proteins self-assemble into VLPs which are empty shells of the HPV virus without the viral DNA and are therefore non-infectious [3].

The serologic antibody response to the vaccines is stronger with higher titers obtained after vaccination than after a natural infection, which is likely due to the specific adjuvants, the strong immunogenicity of the VLPs as well as the route of administration [3]. Vaccine induced protection is thought to be mediated through type-specific HPV antibodies that reach the anogenital area by transudation from serum [30]. It is likely that the higher serum titers result in higher titers in the genital mucosa.

Merck & Co, Inc. has conducted multiple immunogenicity studies and clinical trials examining the efficacy and tolerability of the vaccine. Immunogenicity results showed that administration of a three-dose regimen (0, 2, 6 months) of qHPV (Types 6, 11, 16, 18) L1 VLP vaccine 20/40/40/20 mcg generates robust anti-HPV 6, 11, 16, and 18 responses 4 weeks after the completion of the vaccination regimen and durable anti-HPV 6, 11, 16, and 18 responses 2.5 years following completion of the vaccination regimen. Efficacy results showed that administration of a three-dose regimen of the vaccine substantially reduced the risk for acquisition of persistent HPV 6-, 11-, 16-, or 18-related infection.

Immunogenicity results of a substudy with adults and adolescents showed that for each of the four HPV types, the vaccine induced numerically higher HPV 6, 11, 16, 18 geometric mean titers (GMTs) 4 weeks post dose 2 (month 3) and 4 weeks post dose 3 (month 7) in 10 to 15 year old male and female subjects than in 16 to 23 year old female subjects. Further analyses showed that lower dose formulations of qHPV vaccine induced anti-HPV responses at month 7 that were statistically noninferior to those generated following administration of a three-dose regimen.

When given to HIV-uninfected women without prior exposure to HPV-16 and -18, the qHPV vaccine demonstrated 98% efficacy in preventing cervical intraepithelial neoplasia related to the vaccine types [31] and 100% of anogenital warts [32]. In a trial of 4065 healthy boys and men 16 to 26 years of age, the efficacy of the vaccine was 90.4% in preventing external genital lesions due to the vaccine types [33] and among 602 men who have sex with men, the efficacy against anal intraepithelial neoplasia associated with the vaccine types was 77.5% [34]. The use of the vaccine among 700 black women prevented 100% of cervical and vulvar disease [35].

The very high efficacy rates of the vaccine in preventing disease related to HPV infection in reported in these trials are noted among participants without prior exposure to the vaccine types, either by genital HPV typing or HPV serology. In the Future II trials, the efficacy fell

to 44% for the population of all women who had undergone randomization, which also included subjects who had HPV-16 or 18–related cervical intraepithelial neoplasia or infection with HPV-16 or 18 before the first injection [31].

Despite the overall high HPV burden among HIV-infected women, the majority of women do not have all four vaccine related HPV types. In a study of 146 treatment naïve women initiating cART, the seroprevalence of HPV types 16 and 18 was 16% and 11%, respectively, at baseline [36]. Additionally, in the HER study, among 767 HIV-infected and 390 uninfected women, the DNA prevalence of one or more of HPV types 6, 11, 16, and 18 was 15.9% in HIV-infected women and 6.7% in HIV- uninfected women; specifically, type 6 was 3.1%, 11 was 0.9%, 16 was 5.7%, and 18 was 6.1% [10]. In the SUN study, no women had all 4 vaccine-specific HPV types in either the anus or cervix by DNA testing and only a small fraction had both types 16 and 18 at either anatomical site; most women had only one or neither of the two types detected [17]. Thus, although HIV-infected women have a much higher prevalence of these four types than HIV- uninfected women, the majority of them do not have the types contained in the vaccine. By serological antibody testing in a recent vaccine immunogenicity trial among HIV-infected women, only 4% of the participants had evidence of prior exposure to all 4 vaccine associated HPV types, either due to lack of prior HPV exposure or due to loss of serum HPV antibodies. This suggests that the majority of HIV-infected women, regardless of immune status, would benefit from the vaccination series [37].

Immune responses after vaccination in HIV-infected individuals

Poor responses to standard vaccination series have been documented in HIV-infected patients. Immunogenicity studies of hepatitis A vaccination in HIV-infected patients using the standard vaccination series revealed a low response rate of 48- 64% [38, 39]. Similarly, HIV-infected patients respond to Hepatitis B vaccinations at lower rates, 17-56% compared with 90% in HIV-uninfected persons . In the HIV-infected population, there is evidence to suggest that an adequate antibody response may not be sustained over time as expected [40]. The presence of low-level HIV viremia has been consistently associated with failure to respond to hepatitis vaccination [41]. In HIV-infected children, an undetectable HIV viral load and CD4+ T cell percent greater than 20% predicted a better response to hepatitis A vaccination[42]. There is also a strong association between plasma HIV viral load and primary responses to the live attenuated varicella-zoster vaccine [43] and to live attenuated or inactivated seasonal influenza vaccines [44].

Immunogenicity of the Quadrivalent HPV Vaccine among HIV-Infected Persons

To date, there is limited data available on the efficacy of the vaccine among HIV-infected women but there have been several studies published on the immunogenicity and safety of the currently approved HPV vaccine among HIV-infected women and Table 1 summarizes studies that included women.

In a study conducted by the AIDS Clinical Trials Group (ACTG) to evaluate the immunogenicity and safety of the qHPV vaccine among women aged 13 to 45 years who were seronegative for the HPV types included in the vaccine, the seroconversion rates were >75% for all 4 HPV types [37]. This trial stratified women into three groups depending on the entry CD4 cell count: women with a CD4 count ≤200 cells/μL, >200 to ≤350 cells/μL, and >350 cells/μL. Seroconversion proportions were higher among women with baseline CD4 cell counts >200 cells/μL compared with ≤200 cells/μL. This is consistent with observations from immunogenicity studies of other vaccines (e.g., hepatitis A and B) but is a new finding for the HPV vaccine. Among women with CD4 counts ≤200 cells/μL, women with HIV RNA load <400 copies/mL at baseline had better seroconversion proportions for HPV types 11, 16, and 18 compared with women with viral loads ≥400 copies/mL [37].

The odds of seroconversion were significantly higher for HPV types 6, 11, and 16 compared with type 18 as measured by cLIA [37]. This finding is consistent with other studies and may be related to the assay used and not due to an inherent difference in immunogenicity between HPV types [45, 46].

For women seropositive for the given HPV types prior to the vaccination series, the vaccine induced a significant increase in antibody levels. The antibody concentrations or GMTs induced by the quadrivalent HPV vaccine were significantly higher than those induced by natural HPV infection. The GMT levels among the women with CD4 cell counts >200 cells/μL were similar to those found in HIV-infected men with comparable CD4 cell Among women with CD4 cell counts <200 cells/μL, there was a trend for lower titers compared with higher CD4 cell counts, with a statistical significance noted for only HPV-6 [37]. When compared with published data on HIV-uninfected women, the anti–HPV-16 and -18 GMT in HIV-infected women was almost half that of HIV uninfected women in similar age groups (GMT range, 571–1200 mMU/mL for HPV-16 in our study vs. 2134 mMU/mL in the literature)[47]. The clinical significance of this finding is unclear as the protective titers of HPV antibodies are not defined.

The qHPV vaccine was found to have similar immunogenic efficacy in HIV-infected adolescent and young adults with a CD4 cell count over 350 cells/mm^3 as in healthy controls matched for age and gender with seroconversion rates of 85% among HIV-infected and 91% in HIV-uninfected. The study included both males and females and no mention was made of gender differences in immunogenicity [48]. In a study from South Africa among females 18 to 25 years of age with high exposure rates to HPV 16 and 18 at baseline (up to 85%), the bivalent vaccine was found to be safe. The anti HPV-16 and 18 GTMs at month 7 were 124- and 90-fold higher than those reported in healthy women aged 15–25 years who had cleared a natural infection and noted to be at levels associated with protection against infection and associated lesions due to the vaccine types in healthy women [49].

In a study conducted by the Adolescent Medicine Trials Network for HIV/AIDS Interventions, 99 women aged 16-23 years were enrolled and vaccinated with the qHPV vaccine and immune responses were compared to a historical HIV-negative control. Seroconversion rates were 100% for HPV-6, -11, -16, and -18 among participants taking cART. Rates ranged from 92.3% (for HPV-18) to 100.0% (for HPV-6) among participants

not taking cART. Of note, no differences in GMTs were noted among participants taking cART vs. the comparison group, but GMTs were lower in participants not taking cART vs. the comparison group for HPV-16 (2393 vs. 3892 mMU/mL) and HPV-18 (463 vs. 801 mMU/mL) [50].

In a study undertaken by the IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials) group to evaluate the safety and immunogenicity of the quadrivalent HPV vaccine in HIV-infected preadolescent girls and boys who were 7-12 years of age with a CD4% ≥15, the rate of seroconversion was 90-100% [51]. This response was consistent with the rates of seroconversion reported in HIV-uninfected male and female adolescents and young adult women [52]. Among the HIV-infected children, the GMTs achieved were >27 to >262-fold higher than the seropositivity cutoff, but there was a type dependent difference. The antibody levels achieved against HPV types 6 and 18 were 30-50% lower than those achieved in historical controls, yet for HPV type 6, the antibody levels were similar to HIV-uninfected women 16-20 years old and for the other 3 vaccine HPV types the levels were higher in children compared with the older women, in whom the vaccine has proven to be effective in preventing HPV-related diseases [51].

Vaccine Uptake

According to the Centers for Disease Control and Prevention, the majority of HPV vaccine administered in the US is the qHPV vaccine with delivery occurring mostly by primary care providers or in community health clinics [53]. The vaccines are available to the pediatric population through the Vaccines for Children Program for uninsured or other eligible children [54]. Additionally, as part of the Affordable Care Act of 2013, private health plans and plans obtained from health insurance exchanges starting in 2014 must offer vaccines recommended by the American Council of Immunization Practices to beneficiaries free of charge [55].

HPV vaccination coverage with at least 1 dose among girls aged 13–17 years increased from 25.1% in 2007 to 53.0% in 2011 and remained stagnant in 2012 [56]. In 2013, at least 1 dose coverage and 3 dose coverage increased slightly; among girls aged 13–17 years 57.3% had received at least 1 dose and 37.6% had received all 3 doses [53]. However, there is a large discrepancy in vaccine administration state to state, with at least 1 dose vaccine coverage ranging from 39.9% to 76.6% [57]. Parents who did not or were uncertain regarding vaccinating their daughters reported a lack of knowledge about the vaccine, the vaccine not being recommended by their provider, concerns about safety, and the perception that the vaccine was not needed [53]. In males, at least 1 dose coverage among boys aged 13–17 years increased from 8.3% in 2011 to 20.8% in 2012 and further increased to 34.6% in 2013 [53].

There is a paucity of data on HPV vaccine uptake among HIV infected patients including women outside of clinical trials. Most studies on HPV vaccine in the HIV infected populations focus on immunogenicity and safety. To our knowledge, there are no specific studies on vaccine uptake in HIV infected women. There is a phase III study underway on the use of quadrivalent HPV vaccine in MSM with HIV infection and women over the age of

27. This will address the problem of vaccinating adults who are HIV infected who are older and who have had prior exposure to HPV [58].

Expert Commentary

The burden of HPV infections and HPV-associated diseases is higher in HIV-infected women compared with HIV-uninfected women. Despite the immunologic reconstitution associated with the use of combination antiretroviral therapy (cART), the prevalence of anogenital HPV infections and diseases remains high [14, 15, 17]. Current cervical cancer prevention strategies are aimed at secondary preventions with early detection and treatment of intraepithelial lesions due to HPV infection, and to date there is no consensus in the literature on how to implement anal cancer prevention among women. Primary prevention of HPV infection through vaccination is therefore critically needed.

Women living with HIV infection face unique barriers to HPV vaccination. The quadrivalent HPV vaccine directed against HPV types 6, 11, 16, and 18 has been proven to be both safe and immunogenic in HIV-infected women and it is very likely that its efficacy in preventing HPV-related diseases is as good in HIV-infected women as it has been proven in the general population even though to date no efficacy data have been published from HIV-infected individuals. The duration of adequate antibody titers to the vaccine associated HPV types remains to be established as it will inform providers about the need for boosting vaccine dosing. Studies are underway to evaluate the duration of antibody titers among HIV-infected individuals. There are several challenges facing the medical community. Even in the general population the vaccine uptake among children has been very low [59]. It is unclear what the vaccine uptake is among HIV-infected women, the majority of whom are older than the population targeted for the quadrivalent vaccine. The vaccine is approved for use among women up to 26 years of age. There is lack of data on HPV vaccination rates among younger HIV perinatally infected girls. Among newly diagnosed HIV infected women, 78% are 25 years of age and older [60]. Most women living with HIV infection would therefore not be offered the vaccine. The vaccine age cutoffs come in part from studies among women aged 24-45. Among these women, the vaccine did not prevent high-grade CIN overall. It was only in a subset of women who did not have the vaccine types that the vaccine efficacy remained high [61]. Most HIV-infected women up to the age of 45 do not have prior exposure to all of the vaccine types (either by genital DNA testing or serology), so some protection from the vaccine is to be expected [37]. Further studies are needed to evaluate the benefits of the HPV vaccine among HIV infected older persons.

The cost of the HPV vaccine can be a limiting factor as well as the socio-political resistance to primary prevention. HPV vaccine coverage among underserved populations has been described in the general public. In a study from England, black women or women from other ethnic backgrounds were less likely to get the vaccine compared with white participants [62]. Racial/ethnic minorities, immigrants and low-income women are overrepresented among HIV-infected persons and to our knowledge, no studies have been published on the HPV vaccine uptake among these underserved women.

Strategies to improve vaccination are multifactorial and include several aspects of care. Many of these studies come from HIV uninfected populations so there are challenges in the use of these strategies in HIV infected women. One is patient identification. It is imperative that providers recognize and are familiar with the increased burden of HPV related diseases among women with HIV infection. Data outlined in this review have shown that the vaccine is safe and immunogenic in HIV-infected women. Establishing a routine practice to vaccinate them with the HPV vaccine is important and electronic health record-based interventions can be utilized to achieve this goal. Studies have found that an electronic health record-based intervention was helpful in initiating HPV vaccination and automated educational reminders were effective in promoting completion of the vaccine series [59, 63]. In the US, most clinics are utilizing a form of electronic records and including the HPV vaccine reminders into the system should be emphasized. Educational strategies can also be improved, both to health care providers and women living with HIV. A variety of tools are available for the general population; the CDC has a tip sheet for health care providers to better communicate with families [59, 64]. To target women living with HIV infection these should be modified to specifically address issues and challenges unique among them. Completion and practice-based strategies for improved vaccination uptake can also be tailored for women living with HIV infection. HIV infected women who are doing well with HIV treatment are now being seen every 6 months for follow up visits. In order to complete the vaccine series an extra clinic visit would be needed. Furthermore, many patients are being seen by multiple providers, general practitioners and HIV specialists. It may be unclear whose role it is to vaccinate HIV-infected women and this needs to be addressed as a practice based problem with an emphasis on communication between different providers caring for women living with HIV-infection

Five-year View

There is a need for HPV vaccine efficacy studies among HIV-infected women, including women who are older than 26 years of age. Currently, all females are offered the vaccine regardless of HIV status as HIV testing is not a pre-requisite for HPV vaccination. Therefore, uptake specific to HIV-infected girls and women needs to be determined. Gaining a better understanding of the kinds of obstacles facing HIV-infected women when offered the HPV vaccine would aid in increasing vaccine uptake. Without data specific to HIV infected women, it can be difficult to convince patients to receive the vaccine and for providers to recommend the vaccine. The Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents updated the recommendations in 2013 to include the use of HPV vaccination among HIV infected young men and women aged 13 to 26 years [65].

There are several recent developments with regard to HPV vaccines. First, in December 2014, a new HPV vaccine was approved with increased number of oncogenic HPV types included in the vaccine. This 9-valent HPV vaccine has HPV types 31, 33, 45, 52, and 58 in addition to the types found in the qHPV vaccine, named Gardasil 9™ (Merck & Co., Inc.) (nHPV vaccine). The added types could increase type specific protection from 70% to 90% of HPV types that cause cervical cancer. The nHPV vaccine has comparable immunogenicity rates to that of the qHPV vaccine for the 4 types found in both vaccines and

prevents genital disease and infectioun associated with HPV-31, 33, 45, 52, and 58 [66]. It is well tolerated if administered with Menactra® (Neisseria meningitidis serotypes A, C, Y and W-135 vaccine) and Adacel® [diphtheria, tetanus and acellular pertussis vaccine]) [67]. The HPV9 has not been evaluated among HIV-infected individuals.

A prophylactic L2 vaccine which could potentially prevent all HPV types has been problematic due to poor immunogenicity but could be promising for the future. Similarly several studies evaluating therapeutic vaccines have not been successful.

Reducing the number of HPV vaccine doses from three to two doses may afford sufficient protection against HPV infection and have important public health implications [68]. The European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion, recommending approval of a two-dose schedule for the bivalent HPV vaccine Cervarix in girls aged 9 to 14 years [69]. Two doses of q-HPV given six month apart were found to be immunogenic in girls 9 to 13 years of age [70], irrespective of age, menarchal status or BMI [71] and the two-dose regimen is potentially associated with a substantial reduction in risk of genital warts [72]. Alternative dosing regimens among HIV-infected individuals need to be explored.

Health care professionals may have unclear understanding of HPV vaccine policies. Post marketing misinformation from various sources may play an integral role in shaping decisions about vaccinations [59]. There is an urgent need to better understand the barriers/facilitators to HPV vaccination among HIV-infected individuals

In developing countries, the burden of HPV and related diseases remains even higher than in the United States. The use of the vaccine is limited in these countries due to cost and there is little data on the vaccine uptake and use among HIV infected women living in this resource limited settings.

For children in the general population, school based delivery models for vaccination efforts are associated with improved vaccine uptake compared with clinic-based delivery model [59]. Most HIV infected women are older and no longer in school. In order to ensure adequate HPV vaccine uptake among women with HIV infection other strategies are needed. One is to optimize ways for increased vaccinations during general medical care in clinics. Another option would be to include HPV vaccinations in clinics that provide testing and treatment for HIV and other sexually transmitted diseases.

The role of medical providers who care for HIV infected women is important in ensuring that women receive and complete the HPV vaccination series. It is important that providers are aware of new developments and advances related to HPV vaccination. As more data accumulate on the use of HPV vaccine among HIV-infected individuals, tailoring guidelines accordingly will be important. Several issues specific to HIV infected women need to be answered: First, establishing the timing for booster vaccination among HIV-infected women is needed. Second, approving the HPV vaccine among women older than 26 years of age needs to be evaluated. To date, no recommendations are available for vaccinating HIV-infected women over the age of 27 years. Data suggest that the vaccine is not cost-effective in this group of patients but the data come from modeling based on women who do not have

HIV infection and relatively low-risk populations. Older HIV-infected women should be offered the vaccine off label in certain circumstances as there is some data suggesting that HPV vaccination may prevent reinfection if the vaccine strains have been cleared. Third, recent data show that two-dose regimens may be adequate for protection against HPV infection but more information is needed to implement such a simplified vaccine dosing regimen among HIV infected populations.

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Key issues

- HPV infection and associated diseases remain prevalent among HIV-infected women despite effective HIV treatment
- Natural HPV infection induces a level of antibody production that for most HPV types does not seem to confer protection against subsequent type-specific HPV infection
- Three HPV vaccines are currently approved for use in boys and girls. Bivalent vaccine directed against preventing infection due to HPV types 16 and 18. Quadrivalent vaccine with anti-HPV types 6, 11, 16, and 18. Nonavalent vaccine with anti-HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58
- HPV vaccine is highly effective if given prior to HPV exposure
- HIV-infected women face unique problems with respect to HPV vaccinations. Many of them have been exposed to HPV infection, many are older that the age cut-off for HPV vaccination
- The quadrivalent HPV vaccine has been found to be immunogenic and safe among HIV-infected women
- HPV vaccine efficacy studies among HIV-infected women is needed
- HPV vaccination coverage remains suboptimal in the general population but little is known about HPV vaccination uptake among HIV infected women

Table 1

A Summary of Trials that Included Women Evaluating Safety and Immunogenicity of HPV Vaccines

Authors	Country	HPV Vaccine studied	Outcome evaluated	Population studied	CD4 Cell Count Stratification (N in each stratum)	Placebo controlled	Outcome	HIV-uninfected control included	Safety concerns
Palefsky 2014[73]	India	Quadrivalent	Safety and immunogenicity	150 HIV infected women	Group 1: CD4 nadir ≤ 350, on HAART Group 2: CD4 nadir >350, current CD4 350-500, not on HAART Group 3: CD4 nadir >350, current CD4 >500, not on HAART	No	Seroconversion rates for HPV types 6, 11, 16, 18: 96%, 97%, 99%, 78% respectively	No	No
Kojic 2014[37]	USA, Brazil and South Africa (ACTG)	Quadrivalent	Safety and immunogenicity	315 HIV infected women aged 13-45 years	Stratum A: CD4 >350 (127 participants) Stratum B: CD4 201-350 (95 participants) Stratum C: CD4 ≤200 (93 participants)	No	Seroconversion rates for HPV types 6, 11, 16, 18: Stratum A: 96%, 98%, 98%, 91% respectively Stratum B: 100%, 98%, 98%, 84% respectively Stratum C: 84%, 92%, 93%, 75% respectively	No	No
Giacomet, 2014[48]	Italy	Quadrivalent	Safety and immunogenicity	46 HIV infected and 46 HIV-uninfected males and females aged 13-27 years	No All participants with CD4 ≥350 on HAART	No	Seroconversion rates: 0.85 in HIV-infected	Yes Seroconversion rates: 0.91 in HIV-uninfected	No
Toft 2014[74]	Denmark	Quadrivalent and Bivalent	Safety and immunogenicity Of quadrivalent vs. bivalent vaccine	92 HIV infected men and women 18 years or older	Stratified by use of HAART If on HAART then had a HIV viral load <200 copies Bivalent vaccine: 45 participants Quadrivalent vaccine: 46 participants	No	GMT endpoints Bivalent induced higher anti-HPV 18 titers than quadrivalent vaccine (GMT ratio 4.31) but no difference found for anti-HPV 16 titers. The bivalent vaccine induced higher HPV 16/18 titers in women than men. No gender difference found for quadrivalent vaccine	No	No
Denny 2013[49]	South Africa	Bivalent	Safety and Immunogenicity	120 HIV-infected and 30 HIV uninfected females aged 18-25 yea	No HIV viral load or CD4 cell count stratification. Among the 120 HIV infected women, 3 women had a CD4 cell count <200 (2 in vaccine group, 1 in placebo group)	HIV-infected women were placebo controlled	GMT at one month after completing vaccination series (baseline GMT not reported): HPV type 16: 3558 HPV type 18: 1945 Seroprevalence at baseline high among HIV infected, 73% in placebo group and 85% in vaccine recipients. After vaccination, all women seropositive	GMT at one month after completing vaccination series (baseline GMT not reported): HPV type 16: 8168 HPV type 18: 3703 Seroprevalence at baseline: 63%	No
Kahn 2013[50]	USA and Puerto Rico Adolescent Trials Network (ATN)	Quadrivalent	Immunogenicity and Safety	99 HIV-infected and 267 HIV-uninfected women aged 16-23 years	Stratified by Group A: 69 women not on ART for at least 6 months prior to study entry or naïve to treatment	No	1. GMT (mMU/ML): Group A: For HPV types 6, 11, 26, 18 titers were 658, 727, 2393, 463 respectively Group B	1. GMT (mMU/ML) For HPV types 6, 11, 26, 18 titers were 582, 697, 3892, 801 respectively	One grade 3 adverse event, fatigue

Authors	Country	HPV Vaccine studied	Outcome evaluated	Population studied	CD4 Cell Count Stratification (N in each stratum)	Placebo controlled	Outcome	HIV-uninfected control included	Safety concerns
					Group B: 30 women on antiretroviral therapy (ART) for at least 6 months with HIV RNA plasma loads <400 copes/ml No stratification by CD4 cell count, all participants except one (in group B) had a CD4 count over 200 cells/mm^3		For HPV types 6, 11, 26, 18 titers were 1294, 1522, 5046, 979 respectively 2. Seroconversion rates Group A: For HPV types 6, 11, 26, 18 rates were 100%, 97.1%, 96.4%, 92.3% respectively Group B: Seroconversion rates were 100% for all four HPV types	2. Seroconversion rates were 100% for all four HPV types	
Levin 2010[51]	US and Puerto Rico IMPAACT	Quadrivalent	Safety and Immunogenicity	126 HIV-infected children age 7-12 years	Group 1: CD4% nadir < 15 and CD4% ≥ 15 at screening Group 2: CD4% nadir ≥ 15 and CD4% ≥ 15 and <25 at screening Group 3: CD4% nadir ≥25 and CD4% ≥25 at screening	Yes	Seroconversion rates: Group 1: 100%, 100%, 100%, 90% for HPV types 6, 11, 16, 18 respectively Group 2: 100% for all 4 types Group 3: 100% for all 4 types	No	No