# Chapter 2
# Human Papillomaviruses

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**Core Message** HPV-associated anogenital and oropharyngeal cancers place an enormous burden on the health of populations globally. The natural progression of HPV infection is potentiated by HIV coinfection. Further investigation into site-specific HPV acquisition is vital given the increasing trend in anal and oropharyngeal cancers and the need to inform prevention and treatment. HPV vaccination for both females and males is a promising strategy to prevent HPV infection and potential oncologic sequelae.

## 1 Introduction

Human papillomavirus (HPV) is a major cause of infection related malignancies at multiple anatomic entry sites in both men and women globally. As the most common sexually transmitted infection among men and women worldwide, it is estimated that between 50 and 80 % of men and women will acquire an HPV infection in their lifetime [1]. HPV was first discovered to be an infectious etiological agent of cervical cancer by Harald zur Hausen in the late 1970s, when his laboratory isolated HPV-16 and 18 from cervical cancer biopsies [2]. Overall 4.8 % of all incident cancers globally can be attributable to HPV infection [3] although the fraction attributable to HPV varies by anatomic site. HPV infection has been implicated in nearly 100 % of invasive cervical cancers, 88 % of anal cancers, 70 % of oropharyngeal and vaginal cancers, 43 % of vulvar cancers, and 50 % of penile cancers [3, 4].

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Currently, there are more than 100 fully sequenced HPV genomes that infect the skin and mucosal squamous epithelia. Of these, nearly half have been identified in the anogenital tract [5]. A substantial portion of previous research on HPV has been devoted to understanding the epidemiology of HPV infection, carcinogenesis, screening, and immunization in prevention of cervical cancer. As HPV-associated cervical, anal, and oropharyngeal cancers place an enormous burden on the health of populations globally, more attention has been turned to HPV screening and vaccination. This chapter describes HPV viral structure, molecular biology, and immune response. Additionally, it examines the epidemiology, natural history, and risk factors associated with HPV infection of the cervix, anal canal, and oropharynx including the effects of human immunodeficiency virus (HIV) infection with chronic immunosuppression. Lastly, it discusses treatment modalities and prevention strategies, specifically screening and immunization.

## 2 Virus Structure and Molecular Biology

HPV is a small, circular, double-stranded non-enveloped DNA virus approximately 55 *nm* in diameter [6, 7]. Its DNA genome is approximately 8 kb [8] and contains six nonstructural proteins (E1, E2, E4-E7) that are involved in DNA replication and cell immortalization [1] The virus has two structural proteins, L1 and L2, which are produced late in the infectious cycle; [9] L1 is the major component on the exterior surface of the virion, and L2 is the minor structural protein that typically interacts with L1 and the viral genomic DNA. L1 protein spontaneously self-assembles into capsomeres and virus-like particles (VLPs) when expressed in eukaryotic organisms; thus it is responsible for the initial interaction of the HPV capsid with the host. L2 proteins interact with E2 proteins produced earlier in the viral replication cycle and facilitate transportation of L1 to the nucleus and encapsulation of viral DNA [10–12].

There are more than 100 HPV genotypes that infect the human epidermal or mucosal epithelial cells with varying clinical manifestations and oncogenic potential ranging from benign cutaneous lesions to advanced squamous cell carcinomas of the anogenital and oropharyngeal areas depending on anatomic sites of exposure. These HPV genotypes are divided into low-risk and high-risk categories based on their ability to integrate into host DNA and therefore the potential to produce lesions [13, 14]. Low-risk HPV genotypes such as HPV-6 and 11 do not integrate into the host DNA and are associated with benign warts called condyloma acuminatum, usually found on the oral or genital regions. Other HPV genotypes such as HPV-1, 2, 3, and 10 cause cutaneous lesions, such as common digital warts and flat warts [15]. High-risk genotypes, such as HPV-16, 18, 31, 33, 45, and 56 are commonly found integrated into host DNA and are associated with anogenital lesions that may progress to carcinoma [14]. Currently, there are 13 HPV types, HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 that are designated as carcinogenic [16]. HPV-16 and 18 are the most carcinogenic types, and account for approximately 92 % of anal cancers, 90 % of oropharyngeal cancers, 80 % of vulvovaginal cancers,

70 % of cervical cancers, and 63 % of penile cancers [17]. The attributable fraction of HPV-16 is far greater than HPV-18 at all neoplastic transformation sites [17]. The complex interactions between the HPV genotype, viral genetic variables, host immune response, the phenotype of the infected epithelial cell, and environmental and lifestyle choices impact clinical and microscopic presentation [12, 18].

## 3 Transmission and Immune Response

HPV is highly transmissible through cutaneous and mucosal contact and has a broad incubation period from weeks to years, depending on the amount (dose) of virus transmitted. The infectious period commences when the virus reaches the basal layer of the epithelium, binds, and enters human cells [14, 19]. (Fig. 2.1) [14]. The

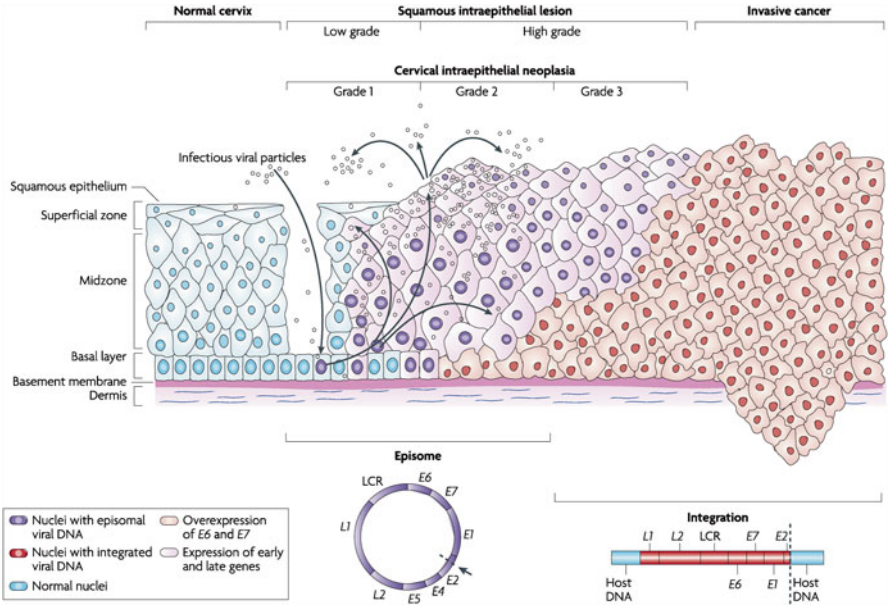


**Fig. 2.1** Human papillomavirus (HPV) induced progression to invasive cervical cancer (ICC). HPV gains entry into the basal cells through microabrasions in the cervical epithelium. Following infection, the early HPV genes E1, E2, E4, E5, E6, and E7 are expressed and the viral DNA replicates from episomal DNA. The viral genome undergoes further replication in the upper mid and superficial layers of epithelium where the late genes L1 and L2, and E4 are expressed. L1 and L2 encapsulate the viral genomes to generate progeny virions. If untreated, the shed virus can initiate a new infection. Viral replication continues in low grade intraepithelial lesions. Some high-risk HPV infections progress from low grade to high-grade cervical intraepithelial neoplasias, and if untreated, some of these lesions progress to invasive cancer. This progression occurs when the HPV genome integrates into the host chromosomes (shown above with red nuclei), accompanied by a loss or disruption of E2, and the subsequent upregulation of E6 and E7 oncogene expression. Reproduced with permission from Woodman et al. [14]

HPV cycle is influenced by the maturity of the infected keratinocyte, as the production of virions is limited to the mature suprabasal epithelial cells [8, 12]. Active replication commences when the basal cells penetrate to the suprabasal compartment and initiates the terminal differentiation program. HPV will replicate and be released into the environment for a variable amount of time, causing viral DNA to be detected [1, 14, 19].

The HPV structural and nonstructural viral regulatory proteins are a result of viral gene expression. The E4 protein is expressed in terminally differentiated keratinocytes in the squamous epithelium, while E1 and E2 are associated with the regulation of viral DNA replication, and early transcription. HPV proteins E6 and E7 that induce proliferation, immortalization, and malignant transformation of cells are critical to viral replication [1, 20]. Their interactions with the proteins pRB and p53 result in multiple mutations that are thought to be the mechanisms of oncogenesis [1]. Such continued activity of E6 and E7 increase genomic instability and result in the accumulation of oncogenic mutations, loss of cell-growth control, and eventually cancer formation. The viral genome eventually integrates into the host genome, providing constant level of E6 and E7 protein activity due to stabilization of the mRNA, further developing the tumor [7, 14, 19, 21, 22].

In a normal host, a cell mediated immune (CMI) response will often clear the virus [22, 23]. Most HPV infections are transient and asymptomatic, over 50% of new infections are cleared in 6–18 months, while 80–90 % can be cleared within 2–5 years through the immune system or other mechanisms [1, 24]. However, in approximately 10–20 % of individuals, and more commonly in those with immune compromise, a failure to develop an effective CMI results in chronic and persistent HPV replication in the host nucleus of a differentiating skin or mucosal epithelial cell. For these individuals unable to clear the virus, HPV infection is likely to progress to clinically or histologically significant lesions [25].

When infection involves oncogenic HPV genotypes, a human host is at greater risk of developing high-grade precancerous lesions that may advance to invasive carcinoma. Such lesions can be understood to be along a histologic continuum of: (1) low grade lesions, where HPV continues to replicate in an episomal state, (2) high grade lesions resulting from viral integration into the host genome, and (3) invasion that can represent oncological transformation [14, 26]. For example, women with a history of genital warts are shown to have an increased risk of progression to stages of cervical intraepithelial neoplasia (CIN1, CIN2, CIN3) and cancer [27].

## 4 Epidemiology of Invasive Cervical Cancer

Invasive cervical cancer (ICC) is the fourth leading cause of cancer in women globally representing 528,000 cases and 266,000 deaths in 2012 [28]. Age-standardized ICC incidence is estimated at 14 per 100,000 women worldwide with incidence rates greater than 30 per 100,000 women in Melanesia and sub-Saharan Africa [28].

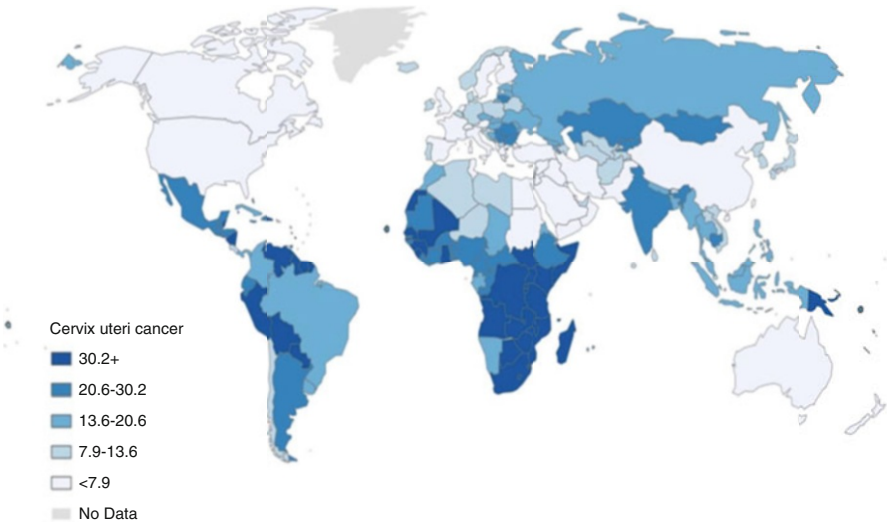


**Fig. 2.2** Age-standardized incidence of cervical cancer worldwide in 2012. Reproduced with permission from GLOBOCAN 2012 [28]

In 2012, 86 % of ICC cases and 88 % of ICC deaths occurred in less developed countries (Fig. 2.2) [28]. In a recent meta-analysis of 194 studies with greater than one million cytologically normal women, HPV prevalence varied from 16 % in Latin America to greater than 30 % among women from Eastern Africa and the Caribbean [29]. HPV-16 was the predominant genotype (3.2 %) followed by HPV-18 (1.4 %), HPV-52 (0.9 %), HPV-31 (0.8 %), and HPV-58 (0.7 %) [29]. Another meta-analysis that included studies comprised of women with normal and abnormal cytology found that HPV prevalence increased with severity of cervical abnormalities [30]. HPV prevalence rose from 76 % in women with CIN1 to 90 % in women with CIN3 [30]. HPV-16 was the most common genotype (63 %) in ICC cases followed by HPV-18 (16 %) and HPV-45 (5 %) [30].

## *4.1 Natural History of Cervical HPV Infection*

HPV prevalence varies with age globally. In Europe and North America, the highest HPV prevalence was among women younger than 25 years old, followed by a gradual decline over time with a lower HPV prevalence in women older than 45 years. HPV prevalence was more constant in women from Asia and Africa, whereas among women from Latin America and the Caribbean, HPV prevalence declined followed by a second prevalence peak during middle age [29].

Although studies in several developed countries show that HPV prevalence can reach 40–80 % in young women 18–25 years old [31–33], many prospective studies have demonstrated that nearly 90 % of women clear these asymptomatic infections

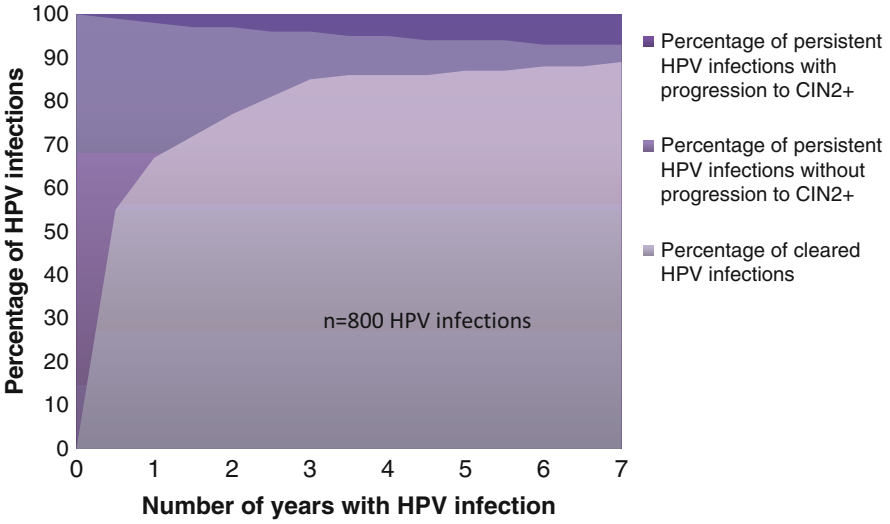


**Fig. 2.3** Clearance, persistence, and progression of human papillomavirus (HPV) infections among 599 women, 18 years and older, from Guancaste, Colombia over 7 years of follow-up from 1993 to 2001. Adapted from Rodriguez et al. [36]

within 2 years [34–36]. Of women with prevalent infections, an estimated 4–10 % have persistent infections that may lead to neoplastic disease [31]. In a subset of 599 women from Guanacaste, Costa Rica, with 800 oncogenic HPV infections and a mean 6.7 years of follow-up, 7 % (58) of HPV infections were persistent with progression to CIN2+ (Fig. 2.3) [36]. The cumulative risk for CIN2+ was 21 % for women with infections that persisted beyond 12 months [36]. Women with persistent infections were older (mean 43 years) compared with those who cleared (mean 23 years). Those with persistent infections also had multiple prevalent infections at baseline. Not all women with persistent HPV infections developed neoplastic disease, but these numbers were small [36].

Despite the extensive research on the natural history of HPV and neoplastic disease of the cervix, there are no well-developed, sensitive tools to detect the exact time at which a high-risk HPV infection transforms into a CIN3+ lesion [24]. Moscicki et al. note that the time to development of a CIN3 lesion is shorter than the decades needed for a CIN3 lesion to progress to complete invasion. In a few aggressive cases, however, CIN3 may progress to early invasive disease. While persistence of HPV infection is critical to the development of neoplastic disease, detection of HPV genotype—including some genetic variants within a genotype—is a better predictor of neoplasia for those with persistent infections [37]. Higher viral loads of oncogenic HPV types are predictive of more severe cytologic abnormalities [24, 38]. Currently, severe neoplastic disease as determined by CIN3 or CIN3+ is the best available clinical surrogate marker of cancer risk, since sometimes CIN2 lesions may result from non-oncogenic HPV types and are often not clearly distinguishable from CIN1 or CIN3 [24].

### *4.2 Risk Factors for Cervical HPV Infection, Persistence, and Progression to Invasive Cancer*

Numerous studies have investigated factors that increase risk of HPV acquisition, persistence, and progression to invasive cervical disease. Younger age at first sexual intercourse is linked to increased HPV acquisition [39]. The high prevalence of infections among adolescents and young adults may be due to immature cervical epithelium (a combination of columnar, squamous, and metaplastic epithelium) as compared to adult women with more impervious squamous cervical epithelium [24, 40, 41]. Of note, most infections are transient in younger populations, and studies have shown that prevalent HPV infections are more likely to persist in women older than 40 years [34]. Rodriguez et al. [34] found that new infections in older women were not associated with CIN2 or severe cervical disease, but instead, prevalent infections were highly correlated with progression to CIN2 or more severe disease, suggesting that persistent infections that were acquired at a young age were more likely to invade [24]. The number of sexual partners, both recent and lifetime, as well as male partner sexual behavior have a strong influence on acquisition of all types of cervical HPV [33, 42–44]. In one study, the risk of HPV detection increased sevenfold among women reporting ≥8 sex partners in their lifetime and increased nearly fivefold among women reporting a new sex partner in 90 days before study enrollment [33, 43]. Likewise, HPV infection increased tenfold among young women whose male partner reported ≥6 lifetime partners [45].

Several studies have also documented the association of cigarette smoking with persistence and development of cervical neoplasia [46–49]. Among women 18–35 years old, the duration of HPV infection was longer at 10.7 months for smokers versus 8.5 months for nonsmokers. A dose response relationship was evident, wherein women who had smoked for greater than 6 years were 60 % less likely to clear an HPV infection [46]. Similarly, women who were former or current smokers were two to four times more likely to develop CIN3 or cancer compared to nonsmokers [47–49]. Long-term oral contraceptive (OC) use has been associated with an elevated risk for persistent HPV infection and progression to invasive cancer [48, 50]. Individual data from 35 studies of women with and without cervical cancer globally showed that the relative risk for cervical cancer increased with current use of oral contraceptives. However, this risk decreased on stopping OC use, and by 10 or more years, risk was similar to that of never-users [50].

## 5 Epidemiology of Anal Cancer

Anal cancers are rare with an age-standardized incidence of less than 2 cases per 100,000 men and women per year, worldwide [51]. They are mostly squamous cell carcinomas arising from the transition zone of the anal mucosa. Almost 90 % of anal cancer cases can be attributed to HPV infection, and HPV-16 is the predominant

genotype (up to 83 %) detected in HPV-positive anal tumors [5]. Globally, in 2002, there were an estimated 99,000 incident cases of anal cancer with slightly more cancers among women (60 %) than men (40 %) [52]. In the USA, there were an estimated 7210 cases of anal cancer and 950 deaths in 2014 [53]. National US data from 2000 to 2010 indicate a rising trend of 2.2 % new cases annually among both men and women [53], with a greater increase among men having sex with men (MSM) and HIV-infected individuals [54]. It has been suggested that the increasing trend in anal cancers is possibly a reflection of the changing sexual practices among men and women and likely potentiated by HIV infection [24]. (Please see section on HPV/HIV coinfection and associated chronic immunosuppression).

Data on anal HPV prevalence among healthy adult HIV-uninfected women and men are limited with most studies reporting anal HPV prevalence in HIV-infected women and men. One of the few studies conducted by Hernandez et al. in Hawaii reported an anal HPV point prevalence of 27 % among 1378 healthy adult women [55]. Other studies of HIV-uninfected women have reported a wide range of anal HPV prevalence from 13 to 56 % [56]. Most of the studies that estimated a high prevalence were among high-risk HIV-uninfected women reporting a history of injection drug use, sexually transmitted infections, and multiple sex partners [56, 57]. Among healthy adult men having sex with women (MSW), findings from two studies, one conducted in the southwest US and the second (HPV in Men (HIM)) study among 1305 heterosexual men from Brazil, Mexico, and the USA revealed that HPV infection in the anal canal was common and anal HPV prevalence ranged from 13 to 24.6 % [56, 58].

## *5.1 HPV Genotype Distribution*

Although most studies have found a similar range of HPV genotypes between the anal canal and cervix, there is relative variation in the frequency of their detection [55, 57]. In the Hawaiian study, among women with concurrent HPV infection, HPV genotypes were slightly more diverse in the anal canal (34 types) than cervix (32 types), but more oncogenic types were detected in the cervix. In contrast, women with only anal and no cervical HPV infection had an almost equal distribution of non-oncogenic (48 %) and oncogenic HPV infections (52 %) with HPV-84 being the most frequently detected genotype followed by 62, 16, 51, and 53. Among women with only cervical HPV infection and no anal HPV infection, HPV-16 was most frequently detected, followed by HPV types 53, 58, 52, and 62. Concurrent anal and cervical HPV infection was observed most commonly in younger women averaging 29 years old [55].

Similar to women, heterosexual men harbored a wide range of HPV types in the anal canal, with up to 34 different genotypes in the HIM study, and HPV 16, 6, and 61 being the most common [58].

## 5.2 Natural History of Anal HPV Infection in Women and Men

Prospective data assessing the natural history of anal HPV infection among women and men show differences in viral persistence. In the Hawaiian cohort, among women followed for a median 15 months, 50 % had an incident anal HPV infection, the majority of which were transient [59]. Of the incident anal HPV infections that cleared, 87 % had cleared within 1 year. Oncogenic anal HPV infections cleared more quickly (median duration 150 days) than oncogenic cervical HPV infections (median duration 8 months) in the same cohort of women [59]. A more recent study of 75 younger women (mean 23.5 years) with a mean follow-up of 7 years found that >80 % of non-HPV-16 high- and low-risk anal HPV infections cleared within 3 years and nearly 24 % of HPV-16 infections persisted beyond 3 years [60]. Among heterosexual men in the HIM study, incident anal infections are much lower at 8.5 per 1000 person months than women in the Hawaii cohort. Most HPV infections including all HPV-16 infections cleared within 6 months with persistent HPV types detected in 4.2 % of men [61].

Conversely, men who have sex with men (MSM) regardless of HIV status have a much higher incidence and persistence of anal HPV infections. In a one-year prospective study of 94 young MSM (mean age 21 years), incident anal HPV infections were high at 38.5 infections per 1000 person months [62]. Nearly 42 % had persistent any type HPV infection, and 19 % had detectable HPV-16 and/or 18. Of those who had prevalent infections at baseline, 81 % cleared one or more types within 6 months. Lifetime number of male receptive anal sex partners was associated with prevalent, incident, and persistent anal HPV infection [62]. Among slightly older HIV-infected MSM (median age 43 years) in Montreal, Canada, the incidence of anal HPV-16 was 10.8 per 1000 person-months, and the cumulative incidence of HPV-16 over 36 months was 33.2 %. Chronic anal HPV-16 infections were the slowest to clear with a mean duration of 36 months [63].

## 5.3 Risk Factors for Anal HPV Infection

Substantive evidence in developed countries supports the link between sexual behavior and anal cancers. Early studies on anal cancers in both men and women found a robust association between a history of sexually transmitted infections and incidence of anal cancer [64, 65] Lifetime number of sex partners (>10), anal intercourse (receptive being higher risk than insertive), and having a partner with a sexually transmitted infection have also been strongly associated with prevalent anal HPV infection and cancer incidence, in addition to other risk factors such as HPV-related cervical neoplasia in women and cigarette smoking [62, 65–68]. Among MSW, data from recent studies indicate that genital HPV infection is a risk factor

for prevalent anal HPV infection. Heterosexual men with genital HPV infection were two to four times more likely to have anal HPV infection [69, 70]. These findings may help explain HPV infection in the anal canal in the absence of receptive anal intercourse in men [56]. Of note, several studies have reported prevalent anal HPV infection in the absence of receptive anal intercourse in both men and women. It has been suggested that in women, a possible transmission route is autoinoculation, wherein the cervix acts as a reservoir for the transmission of HPV through cervico-vaginal fluid to the anus [57]. In addition, hand carriage, the use of objects, and other non-penetrative sexual behaviors may also act as potential modes of transmission [56].

## 6 Epidemiology of Oropharyngeal Cancer

Cancers of the head and neck, specifically oral cavity and oropharyngeal cancers (OPC) that include the tongue base, oropharynx, and tonsils, account for an estimated 400,000 cases and 223,000 deaths in 2008 [71]. HPV has been clearly shown as the causative agent of oropharyngeal squamous cell carcinomas [72] and up to 70 % of OPC are attributed to HPV infection, mostly HPV-16 [4]. In contrast, HPV prevalence is low in the oral cavity, suggesting other etiologic causes [4]. Kreimer et al. suggest that HPV infects the oropharynx because the tonsilar tissue area may resemble the squamous–columnar junction of the cervix with its large, exposed layer of basal epithelial cells [73].

From 1988 to 2004, there was a 225 % increased incidence in HPV-associated OPC in the USA [4]. Similarly, Chaturvedi et al report that from 1983 to 2002, the incidence of OPC increased significantly compared with oral cavity cancers among individuals less than 60 years of age in developed countries most likely due to changes in sexual behavior patterns and thus greater exposure to HPV [74]. OPC incidence was 2–17 times higher in males than in females [74].

Oropharyngeal HPV acquisition and clearance data are limited but initial studies demonstrate that males might be at higher risk than females. Among 5579 male and female participants (14–69 years old) of the US National Health and Nutrition Examination Survey (NHANES) 2009–2010, oral HPV prevalence was significantly higher at 10.1 % in males compared to 3.6 % in females, with an overall population prevalence of 6.9 % and an HPV-16 prevalence of 1 %. Age-specific prevalence showed a bimodal pattern with peak HPV prevalence at 30–34 years and 60–64 years of age [75]. The only prospective study (the HIM Study) showed that for healthy heterosexual men, oral HPV infections are infrequent and transient. Over 1 year, 4.4 % of men acquired a new oral HPV infection, 1.7 % acquired a new oncogenic HPV infection, and 0.6 % acquired a new HPV-16 infection. Oral HPV infections cleared quickly with a median duration of 6.9 months for all HPV, 6.3 months for oncogenic HPV, and 7.3 months for HPV-16, specifically [76].

Risk factors for oral HPV infection include increased lifetime number of vaginal and/or sex partners, oral–anal sexual contact ("rimming"), current tobacco smoking, and immunosuppression as measured by a low CD4 count among HIV patients [72, 75–78].

## 7 Coinfection with HIV and Associated Immunosuppression

HIV-infected men and women are at elevated risk for HPV-associated malignancies at multiple anatomic sites. HIV-infected women share a disproportionate burden of ICC risk with a 2- to 25-fold increase in incident invasive cervical cancers [79]. Furthermore, HIV-infected individuals have a greater than 25-fold increased risk for anal cancer [54] and a 1.3- to 3-fold increased risk for oropharyngeal cancer than HIV-negative individuals [80].

### *7.1 Cervical Cancer in HIV-Infected Women*

HIV-infected women are two to five times more likely to have a cervical HPV infection, experience increased incidence and persistence of HPV, and experience a rapid progression to cervical lesions compared to HIV-negative women. Further, data also indicate that women with HIV have a higher incidence of cervical lesions, recurrent disease, and progression to invasion at a younger age [81–88]. In the USA, the Centers for Disease Control and Prevention (CDC) have designated invasive cervical cancer as an AIDS defining illness [89]. Thus, cervical cancer screening guidelines for HIV infected men and women suggest more frequent screening than within the general population

Cervical HPV prevalence remains markedly higher in HIV-infected women even in the absence of any cervical disease. For example, in a meta-analysis by Clifford et al. that included 20 studies of 5578 HIV-infected women across 5 continents, any type HPV prevalence was 36.3 % in women without cervical abnormalities and 12 % harbored multiple HPV types [90]. HPV-16 was the most common subtype (4.5 %) followed by HPV-58, 18, 52, 31, and 33. HIV-infected women with cervical abnormalities had a twofold to threefold higher HPV prevalence of any type ranging from 69.4 % in ASCUS/LSIL to 84.1 % in HSIL. HPV-16 was the most common type with a prevalence that was almost threefold higher in women with HSIL (31.9 %) in comparison to women with ASCUS/LSIL (12.0 %). Compared to the general female population with HSIL, HIV-infected women with HSIL were more likely to harbor multiple HPV types (41.9 %), exhibit a higher prevalence of HPV types 11, 18, 33, 51, 52, 53, 58, and 61 but a lower prevalence of HPV-16 [90]. In a more recent multicenter study of frozen tissue biopsies from women with cervical carcinoma in Kenya and South Africa, DeVuyst et al. reported a higher HPV-18 prevalence in HIV-positive compared to HIV-negative cases, but the combined prevalence of HPV-16 and/or 18 was similar [91].

## 7.2 Anal Cancer in HIV-Infected Individuals

HIV-infected men who have sex with men (MSM) have the highest anal cancer incidence rates (131/100,000 person-years) in comparison to HIV-infected men who have sex with women (MSW) (46/100,000 person-years), HIV-infected women (30/100,000 person-years) and HIV-uninfected men (2/100,000 person-years) and women (no cases) (Fig. 2.4) [54]. The growing research on HPV infection in HIV-infected MSM supports the high anal cancer incidence estimates. Data from a meta-analysis of 53 studies indicate that the pooled prevalence of anal HPV infection (any type and oncogenic type) was significantly higher in HIV-infected MSM (92 % and 74 %) compared with HIV-uninfected MSM (64 % and 37 %) [92]. A few research studies with HIV-infected MSWs also, report a comparatively lower anal HPV prevalence ranging from 46 to 68 % [93, 94]. Similar to HIV-infected MSM, studies of HIV-infected women in the developed world report an equally high anal HPV prevalence ranging from 79 to 90 % compared with cervical HPV prevalence (53–83 %) in the same population [57, 95]. However, Gonçalves et al. found a similar HPV prevalence across the cervix (61.6 %) and anus (63.7 %) in 138 HIV-infected women from Brazil [96]. Despite the high prevalence of anal HPV, anal cancer incidence is still far lower than ICC incidence suggesting that the natural history of anal HPV infection varies from the cervix and that the process and pathways of carcinogenesis to invasion might be different for the cervix versus the anal canal.

In HIV-infected women and men, HPV-16 is among the most common genotypes to be detected [57, 95–97]. Other HPV types frequently detected in women are 18, 35, 45, 51, 52, 53, 58, 61, and 70 [57, 95, 96]. Two studies that investigated concurrent anal and cervical infection in HIV-infected women found a high concordance

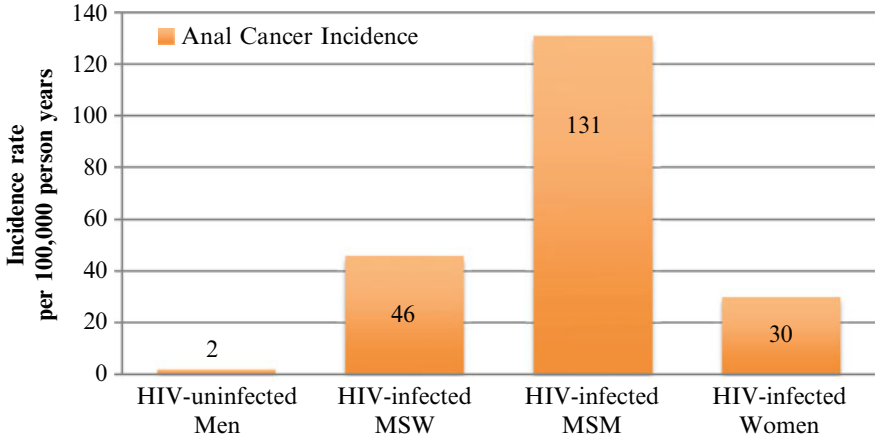


**Fig. 2.4** Anal cancer incidence rate (unadjusted) per 100,000 years among HIV-infected and HIV-uninfected individuals. Adapted from Silverberg et al. [54] Note: No cases among HIV-uninfected women. HIV—human immunodeficiency virus; MSW—men who have sex with women; MSM—men who have sex with men

of HPV genotypes across the cervix and anal canal (63 % and 68.6 %) [95, 96], whereas Palefsky et al. found diverse genotypes between the cervix and anus [57]. In the Hawaii cohort of healthy women, concordance of at least one HPV type across the cervix and anus was 86 % [55]. Among MSM, Machalek et al. reported a pooled anal HPV-16 prevalence of 35.4 % for HIV-infected MSM and 12.5 % for HIV-uninfected MSM [92]. Using PCR testing, Palefsky et al. detected 29 diverse anal HPV types from both HIV-infected and un-infected MSM. Some of the HPV types that were isolated are less frequently detected in the cervix [98].

Although there are limited long-term studies of anal disease, anal cytological abnormalities in both HIV-infected women and men are common. Among 99 women followed prospectively for a minimum of 2 visits and a maximum of 3 visits, the prevalence of anal cytological abnormality was 33 %. HPV was isolated from 67 % of the 33 women. Anal cytological abnormalities consisted of only LSIL and ASCUS. However, of 36 women that underwent high-resolution anoscopy (HRA), 12 were diagnosed with AIN2-3. Incidence of anal abnormalities was 13.1 cases per 100 person-years of follow-up [68]. Similarly, in a study of HIV-infected MSM and MSW, the prevalence of anal cytological abnormalities in MSM was twice (40 %) that of MSW (20 %) [99]. Correspondingly, in a study of 450 HIV-infected MSM in the Spanish AIDS network cohort, slightly more than half (54.7 %) were diagnosed with anal cytological abnormalities that did not include ASCUS. Multiple oncogenic HPV ≥5 types was the only risk factor associated with prevalent anal abnormalities [100]. In Machalek et al.'s meta-analysis, histological high grade AIN pooled prevalence was higher at 29.5 % in HIV-infected MSM versus 21.5 % in HIV-uninfected MSM and anal cancer incidence was eightfold higher among HIV-infected at 45.9 per 100,000 men in comparison to 5.1 per 100,000 in HIV-uninfected men [92].

## *7.3 Oropharyngeal Cancer in HIV-Infected Individuals*

HIV-infection and its associated immunosuppression is clearly one of the risk factors for acquiring an oral HPV infection. Similar to HIV-negative individuals, the natural history of HPV infection in HIV-positive individuals also varies by anatomic site and is influenced by immunosuppression. Data from one study indicated that oral HPV prevalence was significantly higher among HIV-infected women (33 %) than HIV-uninfected women (15 %). However, cervical HPV prevalence was much higher at the same time point in both groups (73 % and 51 %) respectively [78]. Additionally, oral HPV incidence rate in HIV-infected women (3.3 per 100 person months) was twice that of HIV-uninfected women (1.7 per 100 person months). More than half of infections in all women persisted to 6 months [78]. Similarly, another study of HIV-infected men and women found that prevalence (28 % vs 84 %), incidence (31 vs 145 per 1000 person months) and persistence (29 % vs 54 %) were significantly lower for oral HPV infections than anal HPV infections [97].

### 7.4 Antiretroviral Therapy and HPV Infection

Antiretroviral therapy (ART) has had a dramatic impact on morbidity and mortality due to HIV globally. A similar effect has not yet been evident in HIV-infected individuals coinfected with HPV, though theoretically HIV virological suppression and elevated CD4 counts would contribute to a better immune response to increase HPV clearance and decrease acquisition of new infections. Reviews indicate that cervical and anal cancers are not currently declining despite the introduction of ART, but there is insufficient data on the influence of ART on HPV infection and cancer among HIV-infected individuals in the developing world [101–103]. Inconsistent results have been published regarding the effect of ART on the incidence, prevalence, and progression of cervical and anal HPV infections and disease. Some studies show regression of cervical lesions and neoplasias associated with receipt of antiretroviral therapy [104–106], other studies show no such effect [103, 107–109]. Additionally, incidence of anal cancers [110, 111] and oral warts [112] are on the rise among both HIV-positive men and women on ART. Franceschi and Jaffe note that ART-induced immune reconstitution has a modest effect on HPV infection and that the incidence of cervical cancers has not declined in developed nations [113].

The reasons for the limited impact of ART on HPV-related carcinogenesis in HIV-infected individuals are unclear. Palefsky suggests that HIV patients might suffer enough genetic destruction in the epithelium allowing cells to proliferate despite restoration of HPV specific immunity with ART [114]. However, given the relatively recent history of successfully, virologically suppressed HIV and widely available ART, more studies are needed to examine the relationship between immune reconstitution and HPV progression, especially with the confounding factors of ongoing, high-risk behaviors often concurrent in HIV infection. The introduction of the HPV vaccine among HIV infected individuals is also expected to decrease oncologic transformation among this population, with studies forthcoming.

## 8 Prevention of HPV-Related Malignancies

Currently, the two main strategies for prevention of invasive cervical cancer are cervical screening followed by treatment of abnormalities and HPV vaccination. The adoption of cervical screening using Papanicolaou (Pap) testing for the early detection of cervical abnormalities has dramatically decreased the progression to invasive cervical carcinoma worldwide [115]. The two main modalities for cervical screening include: (1) cytology using the conventional Papanicolaou (Pap) test or the newer liquid-based, thin layer cytology which has largely become the standard of care in developed countries, and (2) high-risk HPV nucleic acid testing. In resource-limited settings, particularly in rural areas, the lack of adequate

infrastructure for Pap cytology testing including trained cytopathologists has created a need for alternative visual inspective techniques with acetic acid (VIA) and Lugol's iodine (VILI) that allow same day screen-and-treat approaches [116, 117]. However, due to the subjective nature, quality control issues, and low specificity, solely using visual inspective techniques should be reserved for resource-limited settings [118–121].

## *8.1 Cervical Screening*

### 8.1.1 Pap Cytology Screening

The Pap test, first introduced in 1928 by Dr. Georgios Papanikolaou, utilizes inspection of a smeared cell sample directly onto a glass microscope slide for inspection by a trained cytopathologist. Newer liquid-based cytology (Thin Prep® or Sure Path®) utilizes submerged cervical cell samples within a preservative liquid that is later inspected on a glass microscope slide. The liquid medium removes contaminants, can be performed during menses, and allows the cervical cells to be spread more evenly on the slide. This liquid-cell medium is clinically preferred as it can further undergo HPV nucleic acid testing for high-risk HPV genotypes [115, 122, 123].

### 8.1.2 Screening Using HPV Nucleic Acid Testing

Although Pap cytology has historically been the gold standard for ICC screening, recent evidence indicates that HPV nucleic acid testing is a superior and more cost-effective screening strategy to prevent ICC among women older than 30 years of age, particularly in low and middle-income countries that lack a well-developed infrastructure including well-trained cytopathologists [124–128]. In the USA and other developed countries, HPV nucleic acid testing is recommended in combination with cytology screening and is an invaluable component of cancer screening, management, and treatment. Currently, the FDA has approved four HPV tests: to be used in conjunction with Pap cytology: Hybrid Capture 2®, Cervista®, Cobas, and Aptima® [129]. Aptima® is the only test that detects HPV mRNA, whereas the other three tests detect HPV DNA. These commercially available tests are available from qualitative to semiquantitative platforms and are of two types: (1) tests that detect any of the 12–14 high-risk genotypes and (2) tests that detect HPV-16 or 18 genotypes (Cobas, Cervista™ HR, and most recently Aptima 16,18/45) [130–132]. The Qiagen developed careHPV™ test is a new rapid clinically validated HPV test that can detect any of 14 high-risk genotypes, is able to provide results in a few hours, and is designed specifically for screening women in low-resource settings [124, 133]. It has recently been approved by the China FDA to be used for cervical screening of Chinese women [134].

All of these HPV screening tests are able to detect a small number of HPV genotypes, mainly combined high-risk types or HPV-16/18. For HPV genotyping, other validated molecular assays using type-specific PCR primers that are able to detect a large number of genotypes are mainly used in research facilities [133]. Cuzick et al. note that newer technologies with improved specificity are required to screen high-risk HPV positive women if HPV testing must become an alternate primary modality for screening women [133]. Some potential new approaches could be HPV typing, methylation of host and viral genes, detection of HPV E6 and E7 proteins, and cytologic methods such as $p16^{INK4a}$ staining [133].

### 8.1.3 Cervical Screening Guidelines

Cervical screening guidelines in developed countries differ from developing nations. In the USA, the US Preventive Services Task Force, the American Society for Colposcopy and Cervical Pathology, the American Cancer Society and the American College of Obstetricians and Gynecologists have set the standard for screening guidelines for US women [115, 135]. For women in resource-limited settings, the World Health Organization (WHO) has set the standard and recently updated their guidelines significantly to included specific guidelines for HIV-infected women [136]. (Table 2.1).

In the USA, HIV-negative women between the ages of 30–65 years with a cervix should receive cytology screening every 3 years, or if receiving HPV DNA testing then screening may be extended to 5 years [115]. Women are screened more frequently if HPV positive or abnormal pathology is detected [115, 137]. Women 21–29 years old should receive screening with cytology alone every 3 years if screening results are normal. Screening is not recommended for HIV-negative women under the age of 21. HPV vaccination regardless of HIV status does not change current screening recommendations. For women above the age of 65 who have undergone hysterectomy and/or have no prior history of high-grade cervical lesions may defer HPV screening [115]. (Table 2.1)

As noted earlier, HIV-positive women are at significantly higher risk of progression to cervical carcinoma and should undergo a cervical Pap test at baseline, month 6 and month 12 of first HIV diagnosis; if normal, yearly screens are recommended thereafter regardless of age or modality of HIV acquisition. Immediate referral to colposcopy is recommended for lesions greater than ASCUS [138, 123, 139]. HIV-positive women and high-risk HIV negative women in developing countries should be screened more frequently within 3 years of each negative screening [136].

## *8.2 Prevention of HPV-Related Anal and Oropharyngeal Cancers*

Given the elevated incidence of anal cancers in HIV-positive MSM anal cytology screening is recommended in this population. with frequency of screening currently at the discretion of the health care provider based pathology results [54, 140].

**Table 2.1** Summary of cervical cancer screening guidelines for women by the US Preventive Services Task Force (USPSTF) [135], American Society for Colposcopy and Cervical Pathology (ASCCP) [115], and World Health Organization (WHO) [136]

| Population | USPSTF | ASCCP | WHO[a] |
|---|---|---|---|
| Age <21 years | No screening | No screening | No screening for women <30 years unless HIV+ or living in high HIV prevalence area |
| Age 21–29 years | Cytology screening (Pap smear) alone every 3 years. No HPV screening alone or with cytology. | Cytology screening every 3 years | No screening for women <30 years unless HIV+ or living in high HIV prevalence area |
| Age 30–65 years | Cytology screening (Pap smear) alone every 3 years<br>Cytology and HPV contesting every 5 years (if women prefer to increase screening interval) | Cytology and HPV co-testing every 5 years (preferred)<br>Cytology screening alone every 3 years (acceptable) | Prioritize women 30–49 years[a]<br>Screening interval with HPV testing should be minimum 5 years (not less)<br>Screening interval with VIA/cytology should be 3–5 years |
| Age >65 years | No screening, if adequate prior negative screening and not high-risk for cervical cancer | No screening, if previous history of negative screening<br>Women with prior history of ≥CIN2 must continue routine screening 3–5 years as in women 30–65 years for at least 20 years | |
| After hysterectomy | No screening for women without cervix and no history of ≥CIN2 or cervical cancer | No screening for women without cervix and previous negative screening for CIN2 | |
| HPV vaccinated | | Same as age-specific recommendations for unvaccinated women | |

*VIA* visual inspection with acetic acid, *CIN2* cervical intraepithelial neoplasia grade 2, *ICC* invasive cervical cancer, *HPV* human papillomavirus

[a]WHO guidelines for resource-limited settings with no organized screening efforts

Although formal recommendations as to frequency of screening have not been codified, annual anal screening and referral to high resolution anoscopy (HRA) among HIV-positive MSM and transgendered individuals is now the standard of care in HIV specialty clinics in the USA [141]. Some US facilities are also offering similar annual screening services to all HIV-infected women and men [142]. Unlike in cervical screening, HPV testing has not been validated as a screening tool for anal

precancerous lesions because of the high-prevalence of HPV in the anal canal of high-risk individuals even in the absence of anal abnormalities.

Prevention of oropharyngeal cancer is challenging because of the lack of visibility of precancerous lesions. Although high-risk individuals can be screened for oropharyngeal lesions to detect invasive cancer by visual inspection and cytology, the low sensitivity and specificity of cytology screening studies does not currently justify widespread screening [143, 144]. Oropharyngeal cytology screening is not currently recommended [4, 145].

## *8.3 Treatment of HPV-Related Disease*

Depending on the HPV subtype and location of infection, manifestations can range from simple, isolated lesions to more extensive, clustered lesions necessitating excision. For uncomplicated, external cutaneous HPV condyloma with very mild dysplasia, recommendations are podophyllotoxin (antimitotic agent), imiquimod cream (topical cytokine inducer), or sinecatechins (green tea catechins). For more extensive lesions, cryotherapy using liquid nitrogen, cauterization using trichloroacetic acid or bichloroacetic acid, or traditional surgical excision such as curettage or electrocautery are recommended. For the latest recommendations, dosages, and duration of therapy please refer to the US Centers for Disease Control and Prevention's "Guidelines for the prevention and treatment of opportunistic infections in HIV-Infected Adults and Adolescents." [146]

For more dysplastic lesions such as cervical intraepithelial neoplasia (CIN), anal intraepithelial neoplasia (AIN), vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN), more extensive excision and repeated evaluation is recommended based on the pathological spectrum of atypical cells of uncertain significance (ASC-US), low grade squamous intraepithelial lesion (LSIL), high grade squamous intraepithelial lesion (HSIL), carcinoma in situ, and invasive, squamous cell carcinoma. LSIL includes mild dysplasia (CIN1, AIN1, VAIN1); HSIL includes moderate dysplasia (CIN2, AIN2, VAIN2), severe dysplasia CIN3, AIN3, VAIN3), carcinoma in situ (CIS) [147].

Treatment recommendations depend on pathological grade and patient profile and can include colposcopy (visualization of abnormal cells in the cervical squamocolumnar junction), high resolution anoscopy (HRA), loop electrosurgical excision (LEEP), endocervical curettage (ECC), chemoradiation, or hysterectomy [115, 123, 138]

## *8.4 HPV Vaccination*

A most exciting development for reducing infection-related malignancy are the HPV vaccines (bivalent, quadrivalent and nonavalent), which are estimated to prevent up to 70 % of all cervical and anal cancer cases associated with HPV-16/18

infections and >95 % of genital warts (quadrivalent vaccine) in both women and men globally [31, 148]. A series of clinical trials have shown that both vaccines are highly efficacious in reducing both incident and persistent cervical and vulvovaginal infections and abnormal lesions in women [149, 150], whereas the quadrivalent vaccine has also demonstrated efficacy against persistent genital and anal infection as well as anal lesions in men [148, 151]. The vaccine contains noninfectious and non-oncogenic recombinant L1 proteins that form virus-like proteins (VLPs). These VLPs induce both a humoral response and cell-mediated immune response that is more profound and sustained than natural infection [1, 152].

In 2006, the US Food and Drug Administration (FDA) approved the first quadrivalent (qHPV) vaccine (Gardasil®) that is now recommended for both females and males aged 9 through 26 years to protect against infection from HPV genotypes 6, 11, 16, and 18 [152–155]. Cervarix®) also known as the bivalent HPV vaccine was approved in 2009 by the FDA for the prevention of precancerous lesions and cervical cancer due to HPV types 16 and 18 and is recommended only for females 9 to 26 years old [152, 155]. Both vaccines are administered in three separate shots over 6 months as to ensure high immunogenicity with serum antibodies peaking at 2 years and sustained levels at 5 years [152, 156, 157]. Several clinical trials and other follow-up studies have corroborated that the two vaccines are safe and well-tolerated with limited adverse events, sustained protection of up to 8.4 years and high levels of immunogenicity [31]. Both vaccines have also shown some measure of cross protection against a few HPV types not in the vaccine—HPV 31 for both vaccines and HPV 33 and 45 for Cervarix® [31]. The nonavalent HPV vaccine (Gardasil®9) includes protection against HPV-31, 33, 45, 52 and 58 in addition to the quadrivalent vaccine HPV genotypes of 6, 11, 16 and 18. The Gardasil®9 was recently approved for use in both females and males aged 9–26 years [158]. Recent clinical trial data showed that the nonavalent vaccine was 96 % efficacious against HPV-31, 33, 45, 56, 58 related persistent infection at 6 months, as well as 96.7 % efficacious against related high-grade cervical/vulvar/vaginal disease [159].

### 8.4.1 Impact of HPV Vaccine and Barriers to Implementation

Given that HPV associated anogenital cancers are slow growing, assessing the true impact on incidence of cancers would require future studies. However, a number of recent studies have documented a decreasing cervical HPV prevalence and incidence of cervical abnormalities. In the USA among females 14–19 years old, the prevalence of vaccine HPV types 6, 11, 16, and 18 had decreased from 11.5 to 5.1 % in the post-vaccine era (2007–2010) [160]. Data from Australia and the USA demonstrate a reduction in genital warts in both women and men having sex with women [161–163]. Two other studies among 18–31-year-olds in the USA and <18-year-olds in Australia have documented a decline in the incidence of high grade cervical lesions [164, 165]. A more recent study in Costa Rica demonstrated a vaccine efficacy of 93 % against oral HPV [166] suggesting that the vaccine may have a protective effect against infection at multiple anatomic sites in men and women.

Serrano et al., estimate that the nonavalent vaccine has the potential to prevent up to 90 % of cervical cancers worldwide [167].

There are several challenges for the HPV vaccine to be effective worldwide. The low coverage of HPV vaccinations in the USA as compared to other developed countries is a major challenge. Current data on immunization rates among teens 13–17 year old indicate that slightly more than half (53.8 %) of girls have received one dose of the HPV vaccine and only a third have completed the full three doses [168]. The coverage for males was only 21 % for one dose of the HPV vaccine [167]. For developing countries where the vaccine has the potential to have the maximum impact because of the large burden of ICC, the vaccine is cost prohibitive. In addition, the lack of awareness about the vaccine and its efficacy, concerns about safety, lack of physician recommendations combined with cultural beliefs that adolescents are not sexually active as well as concerns of safety and fear of promiscuity have become major barriers to vaccine uptake in the USA and worldwide [169, 170, 171].

## 9 Conclusion

In summary, HPV-associated cancers are a significant global health burden. Persistent HPV infection with HPV-16 and/or other carcinogenic types has been firmly established as a precursor of cervical disease. Thus, understanding the natural history of cervical HPV infection has been essential to the development of screening and treatment guidelines for the prevention and treatment of cervical cancer. Unlike in cervical cancer, there are relatively few studies that have assessed the natural history of anal and oropharyngeal cancer among women and men. The rising trend in these cancers suggests a critical need for such studies to inform the development of screening and treatment. The vast majority of invasive cervical cancers are among women in developing countries where HIV is also a tremendous burden. While the differences in ICC incidence indicate the lack of widespread availability of preventative services or issues with access when available, HIV must be considered when women present with ICC in these resource-limited settings. Additionally, HIV is a crucial cofactor in the rising incidence of anal cancers among the MSM population as well as in heterosexual men and women. Reducing the high incidence and prevalence of HPV-associated cancers worldwide will require several approaches including prevention of HPV infection, newer screening technologies that can detect precancerous lesions early, and new therapeutics. Meanwhile, HPV vaccination seems to be the most promising in terms of preventing incident HPV infection and its sequelae of HPV-related disease.

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## References


1. Stanley M. HPV - immune response to infection and vaccination. Infect Agent Cancer. 2010;5:19.
2. Pincock S. Virologist wins Nobel for cervical cancer discovery. Lancet. 2008;372(9647):1374.
3. de Martel C, Ferlay J, Franceschi S, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 2012;13(6):607–15.
4. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011;29(32):4294–301.
5. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans: Volume 90 Human papillomaviruses. Lyon: International Agency for Research on Cancer; 2007.
6. Baek JO, Seo JW, Kim IH, Kim CH. Production and purification of human papillomavirus type 33 L1 virus-like particles from Spodoptera frugiperda 9 cells using two-step column chromatography. Protein Expr Purif. 2011;75(2):211–7.
7. Zheng ZM, Baker CC. Papillomavirus genome structure, expression, and post-transcriptional regulation. Front Biosci. 2006;11:2286–302.
8. Longworth MS, Laimins LA. Pathogenesis of human papillomaviruses in differentiating epithelia. Microbiol Mol Biol Rev. 2004;68(2):362–72.
9. Chen XS, Garcea RL, Goldberg I, Casini G, Harrison SC. Structure of small virus-like particles assembled from the L1 protein of human papillomavirus 16. Mol Cell. 2000;5(3): 557–67.
10. Buck CB, Day PM, Trus BL. The papillomavirus major capsid protein L1. Virology. 2013;445(1–2):169–74.
11. Doorbar J. The papillomavirus life cycle. J Clin Virol. 2005;32 Suppl 1:S7–15.
12. Feller L, Khammissa RA, Wood NH, Lemmer J. Epithelial maturation and molecular biology of oral HPV. Infect Agent Cancer. 2009;4:16.
13. Munoz N, Bosch FX, de Sanjose S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003;348(6):518–27.
14. Woodman CBJ, Collins SI, Young LS. The natural history of cervical HPV infection: unresolved issues. Nat Rev Cancer. 2007;7(1):11–22.
15. Bonnez W. Papillomavirus. In: Richman DD, Whitley RJ, Hayden FG, editors. Clinical virology. 2nd ed. Washington, DC: ASM Press; 2002. p. 557–96.
16. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens–Part B: biological agents. Lancet Oncol. 2009;10(4):321–2.
17. Parkin DM, Bray F. Chapter 2: The burden of HPV-related cancers. Vaccine. 2006;24 Suppl 3:11–25.
18. Reichman R. Human papillomavirus infections. In: DL K, E B, AS F, SL H, DL L, JL J, eds. Harrisons principles of internal medicine. Vol 16th ed. New York: Graw-Hill; 2005: 1056–58.
19. Munoz N, Castellsague X, de Gonzalez AB, Gissmann L. Chapter 1: HPV in the etiology of human cancer. Vaccine. 2006;24 Suppl 3:1–10.
20. Munger K, Baldwin A, Edwards KM, et al. Mechanisms of human papillomavirus-induced oncogenesis. J Virol. 2004;78(21):11451–60.
21. Steben M, Duarte-Franco E. Human papillomavirus infection: epidemiology and pathophysiology. Gynecol Oncol. 2007;107(2 Suppl 1):S2–5.
22. Pyeon D, Pearce SM, Lank SM, Ahlquist P, Lambert PF. Establishment of human papillomavirus infection requires cell cycle progression. PLoS Pathog. 2009;5(2):e1000318.
23. Frazer IH. Interaction of human papillomaviruses with the host immune system: a well evolved relationship. Virology. 2009;384(2):410–4.
24. Moscicki AB, Schiffman M, Burchell A, et al. Updating the natural history of human papillomavirus and anogenital cancers. Vaccine. 2012;30 Suppl 5:F24–33.

25. Kanodia S, Fahey LM, Kast WM. Mechanisms used by human papillomaviruses to escape the host immune response. Curr Cancer Drug Targets. 2007;7(1):79–89.
26. Pett M, Coleman N. Integration of high-risk human papillomavirus: a key event in cervical carcinogenesis? J Pathol. 2007;212(4):356.
27. Kjaer SK, Tran TN, Sparen P, et al. The burden of genital warts: a study of nearly 70,000 women from the general female population in the 4 Nordic countries. J Infect Dis. 2007; 196(10):1447–54.
28. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No.11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013: http://globocan.iarc.fr/. Accessed 6 Jan 2013.
29. Bruni L, Diaz M, Castellsague X, Ferrer E, Bosch FX, de Sanjose S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. J Infect Dis. 2010;202(12):1789–99.
30. Guan P, Howell-Jones R, Li N, et al. Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. Int J Cancer. 2012;131(10): 2349–59.
31. Bosch FX, Tsu V, Vorsters A, Van Damme P, Kane MA. Reframing cervical cancer prevention. Expanding the field towards prevention of human papillomavirus infections and related diseases. Vaccine. 2012;30 Suppl 5:F1–11.
32. Dunne EF, Unger ER, Sternberg M, et al. Prevalence of HPV infection among females in the United States. JAMA. 2007;297(8):813–9.
33. Tarkowski TA, Koumans EH, Sawyer M, et al. Epidemiology of human papillomavirus infection and abnormal cytologic test results in an urban adolescent population. J Infect Dis. 2004;189(1):46–50.
34. Rodriguez AC, Schiffman M, Herrero R, et al. Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection. J Natl Cancer Inst. 2010;102(5):315–24.
35. Winer RL, Hughes JP, Feng Q, et al. Early natural history of incident, type-specific human papillomavirus infections in newly sexually active young women. Cancer Epidemiol Biomarkers Prev. 2011;20(4):699–707.
36. Rodriguez AC, Schiffman M, Herrero R, et al. Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. J Natl Cancer Inst. 2008;100(7): 513–7.
37. Schiffman M, Rodriguez AC, Chen Z, et al. A population-based prospective study of carcinogenic human papillomavirus variant lineages, viral persistence, and cervical neoplasia. Cancer Res. 2010;70(8):3159–69.
38. Moscicki AB, Schiffman M, Kjaer S, Villa LL. Chapter 5: Updating the natural history of HPV and anogenital cancer. Vaccine. 2006;24 Suppl 3:S42–51.
39. The International Collaboration of Epidemiological Studies of Cervical C. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: Collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. Int J Cancer. 2007;120(4):885–91.
40. Calore EE, Cavaliere MJ, Calore NM. Squamous intraepithelial lesions in cervical smears of human immunodeficiency virus-seropositive adolescents. Diagn Cytopathol. 1998;18(2): 91–2.
41. Waller J, McCaffery KJ, Forrest S, Wardle J. Human papillomavirus and cervical cancer: issues for biobehavioral and psychosocial research. Ann Behav Med. 2004;27(1):68–79.
42. Almonte M, Albero G, Molano M, Carcamo C, Garcia PJ, Perez G. Risk factors for human papillomavirus exposure and co-factors for cervical cancer in Latin America and the Caribbean. Vaccine. 2008;26 Suppl 11:L16–36.
43. Herrero R, Castle PE, Schiffman M, et al. Epidemiologic profile of type-specific human papillomavirus infection and cervical neoplasia in Guanacaste, Costa Rica. J Infect Dis. 2005;191(11):1796–807.

44. Ho GY, Studentsov Y, Hall CB, et al. Risk factors for subsequent cervicovaginal human papillomavirus (HPV) infection and the protective role of antibodies to HPV-16 virus-like particles. J Infect Dis. 2002;186(6):737–42.
45. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. N Engl J Med. 1998;338(7):423–8.
46. Giuliano AR, Sedjo RL, Roe DJ, et al. Clearance of oncogenic human papillomavirus (HPV) infection: effect of smoking (United States). Cancer Causes Control. 2002;13(9):839–46.
47. Plummer M, Herrero R, Franceschi S, et al. Smoking and cervical cancer: pooled analysis of the IARC multi-centric case–control study. Cancer Causes Control. 2003;14(9):805–14.
48. Luhn P, Walker J, Schiffman M, et al. The role of co-factors in the progression from human papillomavirus infection to cervical cancer. Gynecol Oncol. 2013;128(2):265–70.
49. Castle PE, Wacholder S, Lorincz AT, et al. A prospective study of high-grade cervical neoplasia risk among human papillomavirus-infected women. J Natl Cancer Inst. 2002;94(18): 1406–14.
50. International Collaboration of Epidemiological Studies of Cervical Cancer. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16 573 women with cervical cancer and 35 509 women without cervical cancer from 24 epidemiological studies. Lancet. 2007;370(9599):1609–21.
51. Forman D, de Martel C, Lacey CJ, et al. Global burden of human papillomavirus and related diseases. Vaccine. 2012;30 Suppl 5:F12–23.
52. Giuliano AR, Tortolero-Luna G, Ferrer E, et al. Epidemiology of human papillomavirus infection in men, cancers other than cervical and benign conditions. Vaccine. 2008;26: K17–28.
53. National Cancer Institute. SEER Cancer Statistics Factsheets: Anal Cancer. 2013. http://seer.cancer.gov/statfacts/html/anus.html. Accessed 19 Jan 2014.
54. Silverberg MJ, Lau B, Justice AC, et al. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. Clin Infect Dis. 2012;54(7):1026–34.
55. Hernandez BY, McDuffie K, Zhu X, et al. Anal human papillomavirus infection in women and its relationship with cervical infection. Cancer Epidemiol Biomarkers Prev. 2005;14(11 Pt 1):2550–6.
56. Nyitray AG. The epidemiology of anal human papillomavirus infection among women and men having sex with women. Sex Health. 2012;9(6):538–46.
57. Palefsky JM, Holly EA, Ralston ML, Da Costa M, Greenblatt RM. Prevalence and risk factors for anal human papillomavirus infection in human immunodeficiency virus (HIV)-positive and high-risk HIV-negative women. J Infect Dis. 2001;183(3):383–91.
58. Nyitray AG, Carvalho da Silva RJ, Baggio ML, et al. Age-specific prevalence of and risk factors for anal human papillomavirus (HPV) among men who have sex with women and men who have sex with men: the HPV in men (HIM) study. J Infect Dis. 2011;203(1): 49–57.
59. Shvetsov YB, Hernandez BY, McDuffie K, et al. Duration and clearance of anal human papillomavirus (HPV) infection among women: the Hawaii HPV cohort study. Clin Infect Dis. 2009;48(5):536–46.
60. Moscicki AB, Ma Y, Farhat S, et al. Natural history of anal human papillomavirus infection in heterosexual women and risks associated with persistence. Clin Infect Dis. 2014;58(6): 804–11.
61. Nyitray AG, Carvalho da Silva RJ, Baggio ML, et al. Six-month incidence, persistence, and factors associated with persistence of anal human papillomavirus in men: the HPV in men study. J Infect Dis. 2011;204(11):1711–22.
62. Glick SN, Feng Q, Popov V, Koutsky LA, Golden MR. High rates of incident and prevalent anal human papillomavirus infection among young men who have sex with men. J Infect Dis. 2014;209(3):369–76.
63. de Pokomandy A, Rouleau D, Ghattas G, et al. Prevalence, clearance, and incidence of anal human papillomavirus infection in HIV-infected men: the HIPVIRG cohort study. J Infect Dis. 2009;199(7):965–73.

64. Daling JR, Weiss NS, Hislop TG, et al. Sexual practices, sexually transmitted diseases, and the incidence of anal cancer. N Engl J Med. 1987;317(16):973–7.
65. Holly EA, Whittemore AS, Aston DA, Ahn DK, Nickoloff BJ, Kristiansen JJ. Anal cancer incidence: genital warts, anal fissure or fistula, hemorrhoids, and smoking. J Natl Cancer Inst. 1989;81(22):1726–31.
66. Frisch M, Glimelius B, van den Brule AJ, et al. Sexually transmitted infection as a cause of anal cancer. N Engl J Med. 1997;337(19):1350–8.
67. Melbye M, Rabkin C, Frisch M, Biggar RJ. Changing patterns of anal cancer incidence in the United States, 1940-1989. Am J Epidemiol. 1994;139(8):772–80.
68. Baranoski AS, Tandon R, Weinberg J, Huang FF, Stier EA. Risk factors for abnormal anal cytology over time in HIV-infected women. Am J Obstet Gynecol. 2012;207(2):107.e101–108.
69. Nyitray A, Nielson CM, Harris RB, et al. Prevalence of and risk factors for anal human papillomavirus infection in heterosexual men. J Infect Dis. 2008;197(12):1676–84.
70. Nyitray AG, Smith D, Villa L, et al. Prevalence of and risk factors for anal human papillomavirus infection in men who have sex with women: a cross-national study. J Infect Dis. 2010;201(10):1498–508.
71. Ferlay J, Shin H-R, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127(12):2893–917.
72. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med. 2007;356(19):1944–56.
73. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer Epidemiol Biomarkers Prev. 2005;14(2):467–75.
74. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. J Clin Oncol. 2013;31(36):4550–9.
75. Gillison ML, Broutian T, Pickard RK, et al. Prevalence of oral HPV infection in the United States, 2009-2010. JAMA. 2012;307(7):693–703.
76. Kreimer AR, Pierce Campbell CM, Lin HY, et al. Incidence and clearance of oral human papillomavirus infection in men: the HIM cohort study. Lancet. 2013;382(9895):877–87.
77. Beachler DC, Weber KM, Margolick JB, et al. Risk factors for oral HPV infection among a high prevalence population of HIV-positive and at-risk HIV-negative adults. Cancer Epidemiol Biomarkers Prev. 2012;21(1):122–33.
78. D'Souza G, Fakhry C, Sugar EA, et al. Six-month natural history of oral versus cervical human papillomavirus infection. Int J Cancer. 2007;121(1):143–50.
79. De Vuyst H, Lillo F, Broutet N, Smith JS. HIV, human papillomavirus, and cervical neoplasia and cancer in the era of highly active antiretroviral therapy. Eur J Cancer Prev. 2008;17(6):545–54.
80. Dubrow R, Silverberg MJ, Park LS, Crothers K, Justice AC. HIV infection, aging, and immune function: implications for cancer risk and prevention. Curr Opin Oncol. 2012;24(5):506–16.
81. Hagensee ME, Cameron JE, Leigh JE, Clark RA. Human papillomavirus infection and disease in HIV-infected individuals. Am J Med Sci. 2004;328(1):57–63.
82. Rousseau MN, Costes V, Konate I, et al. Viral load and genomic integration of HPV 16 in cervical samples from HIV-1-infected and uninfected women in Burkina Faso. J Med Virol. 2007;79(6):766–70.
83. Baay MF, Kjetland EF, Ndhlovu PD, et al. Human papillomavirus in a rural community in Zimbabwe: the impact of HIV co-infection on HPV genotype distribution. J Med Virol. 2004;73(3):481–5.
84. Temmerman M, Tyndall MW, Kidula N, Claeys P, Muchiri L, Quint W. Risk factors for human papillomavirus and cervical precancerous lesions, and the role of concurrent HIV-1 infection. Int J Gynaecol Obstet. 1999;65(2):171–81.
85. Gichangi PB, Bwayo J, Estambale B, et al. Impact of HIV infection on invasive cervical cancer in Kenyan women. AIDS. 2003;17(13):1963–8.

86. Hawes SE, Critchlow CW, Sow PS, et al. Incident high-grade squamous intraepithelial lesions in Senegalese women with and without human immunodeficiency virus type 1 (HIV-1) and HIV-2. J Natl Cancer Inst. 2006;98(2):100–9.
87. Vonau B, Boag F. HIV-positive women and cervical screening. Int J STD AIDS. 2000;11(12):767–73.
88. Chin KM, Sidhu JS, Janssen RS, Weber JT. Invasive cervical cancer in human immunodeficiency virus-infected and uninfected hospital patients. Obstet Gynecol. 1998;92(1):83–7.
89. Centers for Disease Control and Prevention. AIDS-Defining Conditions. *Morbidity and Mortality Weekly Report, MMWR.* December 5, 2008;57(RR-10):9.
90. Clifford GM, Goncalves MA, Franceschi S. Human papillomavirus types among women infected with HIV: a meta-analysis. AIDS. 2006;20(18):2337–44.
91. De Vuyst H, Ndirangu G, Moodley M, et al. Prevalence of human papillomavirus in women with invasive cervical carcinoma by HIV status in Kenya and South Africa. Int J Cancer. 2011;131(4):949–55.
92. Machalek DA, Poynten M, Jin F, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. Lancet Oncol. 2012;13(5):487–500.
93. Piketty C, Darragh TM, Da Costa M, et al. High prevalence of anal human papillomavirus infection and anal cancer precursors among HIV-infected persons in the absence of anal intercourse. Ann Intern Med. 2003;138(6):453–9.
94. Sirera G, Videla S, Pinol M, et al. High prevalence of human papillomavirus infection in the anus, penis and mouth in HIV-positive men. AIDS. 2006;20(8):1201–4.
95. Kojic EM, Cu-Uvin S, Conley L, et al. Human papillomavirus infection and cytologic abnormalities of the anus and cervix among HIV-infected women in the study to understand the natural history of HIV/AIDS in the Era of effective therapy (The SUN Study). Sex Transm Dis. 2011;38(4):253–9.
96. Goncalves MA, Randi G, Arslan A, et al. HPV type infection in different anogenital sites among HIV-positive Brazilian women. Infect Agent Cancer. 2008;3:5.
97. Beachler DC, D'Souza G, Sugar EA, Xiao W, Gillison ML. Natural history of anal vs oral HPV infection in HIV-infected men and women. J Infect Dis. 2013;208(2):330–9.
98. Palefsky JM, Holly EA, Ralston ML, Jay N. Prevalence and risk factors for human papillomavirus infection of the anal canal in human immunodeficiency virus (HIV)-positive and HIV-negative homosexual men. J Infect Dis. 1998;177(2):361–7.
99. Darwich L, Videla S, Canadas MP, et al. Distribution of human papillomavirus genotypes in anal cytological and histological specimens from HIV-infected men who have sex with men and men who have sex with women. Dis Colon Rectum. 2013;56(9):1043–52.
100. Gonzalez C, Torres M, Benito A, et al. Anal squamous intraepithelial lesions are frequent among young HIV-infected men who have sex with men followed up at the Spanish AIDS Research Network Cohort (CoRIS-HPV). Int J Cancer. 2013;133(5):1164–72.
101. Bratcher LF, Sahasrabuddhe VV. The impact of antiretroviral therapy on HPV and cervical intraepithelial neoplasia: current evidence and directions for future research. Infect Agent Cancer. 2010;5:8.
102. Palefsky J. Human papillomavirus-related disease in people with HIV. Curr Opin HIV AIDS. 2009;4(1):52–6.
103. Heard I, Palefsky JM, Kazatchkine MD. The impact of HIV antiviral therapy on human papillomavirus (HPV) infections and HPV-related diseases. Antivir Ther. 2004;9(1):13–22.
104. Heard I, Tassie JM, Kazatchkine MD, Orth G. Highly active antiretroviral therapy enhances regression of cervical intraepithelial neoplasia in HIV-seropositive women. AIDS. 2002;16(13):1799–802.
105. Minkoff H, Ahdieh L, Massad LS, et al. The effect of highly active antiretroviral therapy on cervical cytologic changes associated with oncogenic HPV among HIV-infected women. AIDS. 2001;15(16):2157–64.

106. Minkoff H, Zhong Y, Burk RD, et al. Influence of adherent and effective antiretroviral therapy use on human papillomavirus infection and squamous intraepithelial lesions in human immunodeficiency virus-positive women. J Infect Dis. 2010;201(5):681–90.
107. Schuman P, Ohmit SE, Klein RS, et al. Longitudinal study of cervical squamous intraepithelial lesions in human immunodeficiency virus (HIV)-seropositive and at-risk HIV-seronegative women. J Infect Dis. 2003;188(1):128–36.
108. Paramsothy PMPH, Jamieson DJMDMPH, Heilig CMP, et al. The effect of highly active antiretroviral therapy on human papillomavirus clearance and cervical cytology. Obstet Gynecol. 2009;113(1):26–31.
109. Lillo FB, Ferrari D, Veglia F, et al. Human papillomavirus infection and associated cervical disease in human immunodeficiency virus-infected women: effect of highly active antiretroviral therapy. J Infect Dis. 2001;184(5):547–51.
110. Hessol NA, Pipkin S, Schwarcz S, Cress RD, Bacchetti P, Scheer S. The impact of highly active antiretroviral therapy on non-AIDS-defining cancers among adults with AIDS. Am J Epidemiol. 2007;165(10):1143–53.
111. Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. Int J Cancer. 2008;123(1):187–94.
112. Cameron JE, Mercante D, O'Brien M, et al. The impact of highly active antiretroviral therapy and immunodeficiency on human papillomavirus infection of the oral cavity of human immunodeficiency virus-seropositive adults. Sex Transm Dis. 2005;32(11):703–9.
113. Franceschi S, Jaffe H. Cervical cancer screening of women living with HIV infection: a must in the era of antiretroviral therapy. Clin Infect Dis. 2007;45(4):510–3.
114. Palefsky J. Biology of HPV in HIV infection. Adv Dent Res. 2006;19(1):99–105.
115. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. Am J Clin Pathol. 2012;137(4):516–42.
116. Denny L. Prevention of cervical cancer. Reprod Health Matters. 2008;16(32):18–31.
117. Denny L, Kuhn L, De Souza M, Pollack AE, Dupree W, Wright Jr TC. Screen-and-treat approaches for cervical cancer prevention in low-resource settings: a randomized controlled trial. JAMA. 2005;294(17):2173–81.
118. Arbyn M, Ronco G, Anttila A, et al. Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. Vaccine. 2012;30 Suppl 5:F88–99.
119. Sankaranarayanan R, Esmy PO, Rajkumar R, et al. Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. Lancet. 2007;370(9585):398–406.
120. Sankaranarayanan R, Shyamalakumary B, Wesley R, Sreedevi Amma N, Parkin D, Nair M. Visual inspection with acetic acid in the early detection of cervical caner and precursors. Int J Cancer. 1999;80(1):161.
121. Shastri SS, Dinshaw K, Amin G, et al. Concurrent evaluation of visual, cytological and HPV testing as screening methods for the early detection of cervical neoplasia in Mumbai, India. Bull World Health Organ. 2005;83(3):186–94.
122. Ronco G, Cuzick J, Pierotti P, et al. Accuracy of liquid based versus conventional cytology: overall results of new technologies for cervical cancer screening: randomised controlled trial. BMJ. 2007;335(7609):28.
123. Smith RA, Brooks D, Cokkinides V, Saslow D, Brawley OW. Cancer screening in the United States, 2013: a review of current American Cancer Society guidelines, current issues in cancer screening, and new guidance on cervical cancer screening and lung cancer screening. CA Cancer J Clin. 2013;63(2):88–105.
124. Qiao YL, Sellors JW, Eder PS, et al. A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. Lancet Oncol. 2008;9(10):929–36.
125. Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. N Engl J Med. 2009;360(14):1385–94.

126. Flores YN, Bishai DM, Lorincz A, et al. HPV testing for cervical cancer screening appears more cost-effective than Papanicolau cytology in Mexico. Cancer Causes Control. 2011;22(2):261–72.
127. Sroczynski G, Schnell-Inderst P, Muhlberger N, et al. Cost-effectiveness of primary HPV screening for cervical cancer in Germany–a decision analysis. Eur J Cancer. 2011;47(11): 1633–46.
128. Bulkmans N, Berkhof J, Rozendaal L, et al. Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade 3 and cancer: 5-year follow-up of a randomised controlled implementation trial. Lancet. 2007;370(9601):1764–72.
129. American Society for Colposcopy and Cervical Pathology (ASCCP). 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. 2009 addendum. 2009. http://www.guideline.gov/content.aspx?id=14698. Accessed 7 Feb 2014.
130. Cox JT. History of the use of HPV testing in cervical screening and in the management of abnormal cervical screening results. J Clin Virol. 2009;45 Suppl 1:S3–12.
131. Khan MJ, Castle PE, Lorincz AT, et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. J Natl Cancer Inst. 2005;97(14):1072–9.
132. Poljak M, Cuzick J, Kocjan BJ, Iftner T, Dillner J, Arbyn M. Nucleic acid tests for the detection of alpha human papillomaviruses. Vaccine. 2012;30 Suppl 5:F100–6.
133. Cuzick J, Bergeron C, von Knebel DM, et al. New technologies and procedures for cervical cancer screening. Vaccine. 2012;30 Suppl 5:F107–16.
134. Evaluate Ltd. QIAGEN Announces Commercial Launch of CareHPV Test in China. 2013; http://www.evaluategroup.com/Universal/View.aspx?type=Story&id=420248. Accessed 7 Feb 2014.
135. U.S. Preventive Services Task Force. Screening for Cervical Cancer. U.S. Preventive Services Task Force Recommendation Statement. 2012; http://www.uspreventiveservicestaskforce.org/uspstf11/cervcancer/cervcancerrs.htm. Accessed 25 Jan 2014.
136. World Health Organization (WHO). WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. . *WHO Guidelines.* 2013. http://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/. Accessed 10 Feb 2014.
137. Wright TC, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 consensus guidelines for the management of women with abnormal cervical screening tests. J Low Genit Tract Dis. 2007;11(4):201–301.
138. Panel on Opportunitistic Infections in HIV-Infected Adults and Adolescents. *Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.* 2013.
139. Centers for Disease Control and Prevention (CDC). USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immuno-deficiency virus: a summary. *MMWR Morb Mortal Wkly Rep.* 1995;44:1-34.
140. Smyczek P, Singh AE, Romanowski B. Anal intraepithelial neoplasia: review and recommendations for screening and management. Int J STD AIDS. 2013;24(11):843–51.
141. Ortoski RA, Kell CS. Anal cancer and screening guidelines for human papillomavirus in men. J Am Osteopath Assoc. 2011;111(3 Suppl 2):S35–43.
142. US Dept of Health and Human Services (DHHS) Health Resources and Services Administration HIV/AIDS Bureau. Anal Dysplasia. *Guide for HIV/AIDS Clinical Care* 2011; http://hab.hrsa.gov/deliverhivaidscare/clinicalguide11/cg-607_anal_dysplasia.html. Accessed 25 Jan 2014, 2014.
143. Kreimer AR, Chaturvedi AK. HPV-associated oropharyngeal cancers–are they preventable? Cancer Prev Res (Phila). 2011;4(9):1346–9.

144. Fakhry C, Rosenthal BT, Clark DP, Gillison ML. Associations between oral HPV16 infection and cytopathology: evaluation of an oropharyngeal "pap-test equivalent" in high-risk populations. Cancer Prev Res (Phila). 2011;4(9):1378–84.
145. Affairs ACoS. Statement on Human Papillomavirus and Squamous Cancers of the Oropharynx. 2013; http://www.ada.org/1749.aspx. Accessed 9 Jan 2014, 2014.
146. Centers for Disease Control and Prevention. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *Morbidity and Mortality Weekly Report, MMWR*. April 10, 2009;58(RR-4):68.
147. Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda system: terminology for reporting results of cervical cytology. 2002;287(16):2114-2119.
148. Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med. 2011;365(17):1576–85.
149. FUTURE_II_Study_Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. New England J Med. 2007;356(19):1915–27.
150. Paavonen J, Jenkins D, Bosch FX, et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. Lancet. 2007;369(9580):2161–70.
151. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. N Engl J Med. 2011;364(5):401–11.
152. Erickson BK, Landers EE, Huh WK. Update on Vaccination Clinical Trials for HPV-Related Disease. Clin Ther. 2014;36(1):8–16.
153. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2010;59(20):626–29.
154. Markowitz LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER. Quadrivalent human papillomavirus vaccine: recommendations of the advisory committee on immunization practices (ACIP). MMWR Recomm Rep. 2007;56(RR-2):1–24.
155. Centers for Disease Control and Protection (CDC). Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedules for Persons Aged 0 Through 18 Years and Adults Aged 19 Years and Older—United States, 2014. *Morbidity and Mortality Weekly Report*. 2014;Suppl/Vol 63(Feb 7):108-112.
156. Dobson SR, McNeil S, Dionne M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. JAMA. 2013;309(17):1793–802.
157. Roteli-Martins CM, Naud P, De Borba P, et al. Sustained immunogenicity and efficacy of the HPV-16/18 AS04-adjuvanted vaccine: up to 8.4 years of follow-up. Hum Vaccin Immunother. 2012;8(3):390–7.
158. US Food and Drug Administration. FDA approves Gardasil 9 for prevention of certain cancers caused by five additional types of HPV. 2014; http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm426485.htm. Accessed March 8, 2015, 2015.
159. Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med*. 2015;372(8):711–723.
160. Markowitz LE, Hariri S, Lin C, et al. Reduction in human papillomavirus (HPV) prevalence among young women following HPV vaccine introduction in the United States, National Health and Nutrition Examination Surveys, 2003-2010. The Journal of infectious diseases. 2013;208(3):385–393.
161. Donovan B, Franklin N, Guy R, et al. Quadrivalent human papillomavirus vaccination and trends in genital warts in Australia: analysis of national sentinel surveillance data. *Lancet Infect Dis*. 2010.
162. Read TR, Hocking JS, Chen MY, Donovan B, Bradshaw CS, Fairley CK. The near disappearance of genital warts in young women 4 years after commencing a national human papillomavirus (HPV) vaccination programme. *Sex Transm Infect*. 2011;87(7):544–547.

163. Bauer HM, Wright G, Chow J. Evidence of human papillomavirus vaccine effectiveness in reducing genital warts: an analysis of California public family planning administrative claims data, 2007-2010. American journal of public health. 2012;102(5):833–835.
164. Powell SE, Hariri S, Steinau M, et al. Impact of human papillomavirus (HPV) vaccination on HPV 16/18-related prevalence in precancerous cervical lesions. *Vaccine*. 2012;31(1): 109–113.
165. Brotherton JM, Fridman M, May CL, Chappell G, Saville AM, Gertig DM. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. *Lancet*. 2011;377(9783):2085–2092.
166. Herrero R, Quint W, Hildesheim A, et al. Reduced Prevalence of Oral Human Papillomavirus (HPV) 4 Years after Bivalent HPV Vaccination in a Randomized Clinical Trial in Costa Rica. *PLoS One*. 2013;8(7):e68329.
167. Serrano B, Alemany L, Tous S, et al. Potential impact of a nine-valent vaccine in human papillomavirus related cervical disease. *Infect Agent Cancer*. 2012;7(1):38.
168. Centers for Disease Control and Prevention (CDC). National and State Vaccination Coverage Among Adolescents Aged 13–17 Years — United States, 2012. *MMWR Morb Mortal Wkly Rep*. 2013;62(34):685–693.
169. Dorell CG, Yankey D, Santibanez TA, Markowitz LE. Human papillomavirus vaccination series initiation and completion, 2008-2009. *Pediatrics*. 2011;128(5):830–839.
170. Pierce Campbell CM, Menezes LJ, Paskett ED, Giuliano AR. Prevention of invasive cervical cancer in the United States: past, present, and future. *Cancer Epidemiol Biomarkers Prev*. 2012;21(9):1402–1408.
171. Al-Dubai SA, Alshagga MA, Al-Naggar RA, et al. Knowledge, attitudes and barriers for human papilloma virus (HPV) vaccines among Malaysian women. Asian Pac J Cancer Prev. 2010;11(4):887–892.