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Human Papillomavirus Biology, Pathogenesis, and Potential for Drug Discovery: A Literature Review for HIV Nurse Clinical Scientists

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Abstract

Persistent oncogenic human papillomavirus (HPV) infection increases the probability that precancerous anal high-grade squamous intraepithelial lesions will progress to invasive anal cancer. Anal neoplasia associated with HPV disproportionately affects HIV-infected individuals, especially men who have sex with men. Prevention is limited to HPV vaccine recommendations, highlighting the need for new treatments. The purpose of this review is to provide HIV information to nurse clinical scientists about HPV-related cancer to highlight the connection between: (a) HPV biology and pathogenesis and (b) the development of drugs and novel therapeutic methods using high-throughput screening. PubMed and CINAHL were used to search the literature to determine HPV-related epidemiology, biology, and use of high-throughput screening for drug discovery. Several events in the HPV life cycle have the potential to be developed into biologic targets for drug discovery using the high-throughput screening technique, which has been successfully used to identify compounds to inhibit HPV infections.

Keywords

anal cancer; high-throughput screening; HIV; human papillomavirus

Human papillomaviruses (HPV) represent a diverse anthology of medical diseases. The spectrum ranges from benign plantar warts to invasive cancers. The emerging burden of cancer in people living with HIV (PLWH) draws attention to HPV as a growing public health concern. Several factors contribute to the burden, including the lack of screening guidelines, absence of knowledge regarding transmission, minimal prevention methods, and limited clinical signs and symptoms of infection (Brabin, Roberts, Farzaneh, & Kitchener, 2006; Brewer & Fazekas, 2007; Walhart, 2012), which highlights the need to understand the biology and pathogenesis of HPV in order to identify novel interventions to prevent high-risk groups such as PLWH and men who have sex with men (MSM) from developing anal cancer and HPV-related infections.

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Disclosures

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The purpose of this literature review is to provide HIV nurse clinical scientists with an epidemiology background of HPV-related cancer to highlight the connection between: (a) understanding HPV biology and pathogenesis and (b) its role in drug discovery and the development of novel therapeutic methods. The information provided will help HIV nurse clinical scientists contribute to the development of novel treatment interventions. HIV nurse clinical scientists are in a unique position to translate basic science into therapeutic interventions because they address the individual from multidimensional perspectives, and the questions that they generate from clinical settings are often grounded in basic biology. This enables HIV nurse clinical scientists to combine clinical and translational research to directly contribute to the patient's continuum of care.

Background

HIV nurse clinical scientists need to recognize the important role HPV plays in the development of cancer, specifically anal cancer, in PLWH. There are more than 100 types of HPV; subsets of high-risk HPV, specifically HPV-16 and −18, have the ability to induce several types of cancer, including anal cancer (Chen et al., 2014; Da Costa, Hogeboom, Holly, & Palefsky, 2002; Morshed, Polz-Gruszka, Szymanski, & Polz-Dacewicz, 2014). For the purpose of this article, HPV-16 and −18 will be synonymous with HPV.

HPV Epidemiology

HPV is the most common sexually transmitted infection (Hessol et al., 2009). At least 75% of individuals will acquire a genital HPV infection in their sexual lifetimes (Buck et al., 2006; Hessol et al., 2009). In a recent meta-analysis of 157,879 women, the prevalence of oncogenic HPV was reported to be as high as 10% in women with normal cytology, giving an estimate of 600 million infected people (Chen et al., 2014). HPV has the ability to cause precancerous changes in the anal canal, or anal high-grade squamous intraepithelial lesions (aHSIL; Hessol et al., 2009; Palefsky et al., 2011). aHSIL is believed to be the precursor to anal cancer and it has been suggested that persistent infection with HPV can, over time, increase the probability of aHSIL progressing to invasive anal cancer (Hessol et al., 2009; Palefsky et al., 2011). In 2014 it was estimated that, in the United States, the incidence rate of anal cancer was 7,270 (4,630 in women and 2,640 in men) and there were 1,010 deaths (American Cancer Society, 2014; National Cancer Institute, 2014, n.d.).

The presence of HPV is nearly universal within the MSM population and, as a result, aHSIL disproportionately affects MSM who have HIV (Glick, Feng, Popov, Koutsky, & Golden, 2014; Hessol, et al., 2009; Koutsky, 1997). In a meta-analysis by Machalek and colleagues (2012), the prevalence of aHSIL in HIV-infected MSM proved by biopsy was 29%, compared with 22% in HIV-uninfected MSM. In the same meta-analysis, anal cancer incidence was 46/100,000 in HIV-infected MSM per year, versus 5.1/100,000 in HIV-uninfected MSM (Machalek et al., 2012). Additional incidence surveillance data have suggested that HIV infection rates of people with aHSIL are 10–50 times greater in MSM when compared with HIV-uninfected MSM (Hessol et al., 2009). There are several reasons for these data, including sexual behavior, immunosuppression, HIV viral load, length of time

on antiretroviral therapy (ART), and prolonged duration of HIV infection (Duncan et al., 2015; Guiguet et al., 2009; Silverberg et al., 2012; Simard, Pfeiffer, & Engels, 2011).

HPV infection is associated with higher incidence rates of anal cancer in PLWH and MSM, but the direct relationship between HIV and anal cancer has been difficult to separate from the prevalence of HPV in this population (Stanley, Winder, Sterling, & Goon, 2012; Uronis & Bendell, 2007). One reason for this may be that HIV-infected individuals have higher HPV viral loads than HIV-uninfected individuals, with more frequent infections with concomitant multiple HPV types. With multiple HPV types, there is less HPV clearance and thus, more ubiquitous HPV persistent infection (Strickler et al., 2005). As a consequence, HPV incidence rates and prevalence are higher in HIV-infected individuals. This is evidenced by increasing incidences of anal cancer in HIV-infected MSM over the last 2 decades (Da Costa et al., 2002; Hessol et al., 2009; Schwartz et al., 2013; Shiels et al., 2011).

The widespread availability of effective ART beginning in 1996 dramatically decreased the mortality rate of HIV-infected individuals (Simard et al., 2011). Despite overall improved survival, PLWH remain at an increased risk for anal cancer because of prolonged HIV-induced immune suppression and longer life expectancies (Pokomandy et al., 2011). Longer life expectancies suggest PLWH are more likely to be affected by diseases that manifest more slowly, such as anal cancer, while maintaining a regimen of ART (Duncan et al., 2015; Pokomandy et al., 2011).

HPV Prevention

Current HPV prevention methods for sexually active individuals are limited. This is due, in part, to the lack of signs and symptoms of HPV infection and a general absence of understanding and knowledge about the transmission of HPV infection in the general public (Morshed et al., 2014; Palefsky et al., 2011; Palefsky, Berry, & Jay, 2012). What we do know is that HPV is transmitted through microtraumas or tears in the epithelium during intercourse. A practical HPV prevention intervention would be the use of a lubricant to help reduce the risk of microtraumas associated with intercourse. However, if one does not know s/he is infected with HPV, because of the lack of presenting signs and symptoms, or understand how easy it is to transmit HPV from one sexual partner to the next, there is simply no consideration to protect him-/herself and others.

The recent availability of several HPV vaccines (i.e., quadrivalent and 9-valent) have emerged as potentially important strategies for HPV prevention (Merck and Co., Inc., 2014; Palefsky et al., 2011). Commercially available HPV vaccines can provide coverage against HPV types 16, 18, 31, 33, 45, 52, and 58 for prevention of cancer, and HPV types 6 and 11 for prevention of genital warts (Merck and Co., Inc., 2014). They are considered to be safe, easy to produce, and stable (Palefsky et al., 2011). However, there are several limitations to the vaccine. It is expensive, and it is recommended that it be administered between the ages of 9 and 26 years, and prior to sexual debut (Huang et al, 2012; Palefsky et al., 2011). The age and sexual debut restrictions on the administration of HPV vaccines create a gap in the continuum of care for anyone ages 26 years and older and anyone who has achieved sexual debut (Palefsky et al., 2011). Additionally, condoms demonstrate limited efficacy in

preventing HPV transmission because condoms do not fully cover the penis and perianal areas, allowing for contact transmission on exposed areas with a sexual partner (Brewer & Fazekas, 2007). It remains worthwhile to investigate other interventions to provide individuals with protection against HPV, particularly therapeutic compounds that target HPV types not currently covered by vaccine.

High-Throughput Screening Techniques

One way to identify new prevention strategies is to build on advances in the field of HPV biology at the cellular and molecular levels. HPV biologists now have models to describe the complex life cycle and pathogenesis of HPV. HIV nurse clinical scientists can use knowledge of the complex HPV life cycle to aid in the discovery of novel therapeutic compounds by high-throughput screening (HTS) techniques. HTS is a proven pharmacology technique to identify small molecules and compounds that have the potential to be developed into new therapeutic interventions. The process involves developing a measurement tool (referred to as an assay) designed for a specific biologic target (i.e., kinase-inhibitor, binding sites, or enzyme) in a 96-well plate. Once the assay has been optimized in a 96-well plate, it is scaled up or miniaturized to a 384-well plate format. The miniaturization of the assay allows automated liquid-handling robots to rapidly prepare the plates and scan a library of thousands and thousands of small molecules and compounds.

HTS is becoming increasingly more common among clinicians and scientists interested in identifying small molecules or bioactive compounds appropriate for drug development and clinical application. HTS has the potential to be used to identify compounds able to modulate HPV infection (Buck et. al., 2006; Huang et al., 2012). Identification of these compounds is the first step in the development of new drugs for treatment and prevention. An example of a prevention intervention in sexually active individuals would be a personal lubricant or mouthwash combined with a compound able to block HPV from infecting cells. Novel interventions such as a personal lubricant or mouthwash would expand clinical abilities to provide prevention and patient care for both PLWH and MSM.

Summary

HPV is the most common sexually transmitted infection. The HPV co-infection in PLWH, especially in MSM, increases the risk of acquiring aHSIL and its development into anal cancer. The epidemiology of HPV is critical to framing the answer to “why we care” and promoting the discovery of new therapeutic methods. The key to discovering new therapies is to understand the intricate and complex biology and pathogenesis of HPV. The knowledge of HPV biology and pathogenesis will help identify potential biologic targets (i.e., phases in the cell cycle, gene expression, or capsid formation). Biologic targets can be developed into assays that can be used with HTS to assist in drug discovery.

Methods

The field of HPV research is large and multifaceted, represented by HPV biologists, clinicians, and researchers. This review of the literature focused on the specific niche between the relationship of HPV biology/pathogenesis and the use of HTS for drug

discovery. The literature will be grouped according to: (a) biology/pathogenesis of HPV, and (b) use of HTS screening for HPV drug discovery. The databases PubMed and CINAHL were selected because of PubMed's broad scope of basic science research and CINAHL's focus on nursing research. PubMed and CINAHL were searched using the following inclusion criteria search and MESH terms: HPV, aHSIL, anal cancer, HIV, HPV biology, HPV pathogenesis, high-throughput screening, and HPV drug discovery. Articles focusing on the following were excluded: condylomata acuminata, abnormal cytology, vaccine titers, genotyping, HPV biology only in females, HPV head and neck cancers, basic viral infection, proctology, and herpes simplex virus. Table 1 summarizes the relevant literature applicable to the purpose of this article.

Results

HPV Biology and Pathogenesis

A brief primer of HPV biology will be presented to lay the foundation to discuss the relationship between HPV biology/pathogenesis and drug discovery. HPV is a small double-stranded DNA nonenveloped virus and has a unique and complex viral life cycle among viruses. This is because HPV viral replication is tightly linked to the differentiation of epithelial cells in the host (Day & Schelhaas, 2014; Pyeon, Pearce, Lank, Ahlquist, & Lambert, 2009). In order for progeny virus to form, HPV must: (a) establish viral DNA in mitotically active basal cells in the stratified epithelium, (b) facilitate maintenance of viral DNA at low copy numbers in dividing epithelial cells, and (c) promote high copy number DNA amplification and encapsidation as the cells migrate up the epithelium where terminally differentiated (nondividing) epithelial cells are located to produce viral progeny (Doorbar, 2006; Middleton et al., 2003; Pyeon et al., 2009).

Several naturally occurring events in the HPV life cycle have the potential to be developed as biologic targets for HTS drug discovery. The HPV viral gene, E2, is one such example. E2 plays a critical role in viral transcription, replication, and maintenance of the viral genome. E2 is a DNA-binding site that recognizes E2 binding during transcription. Additionally, E2 has transcriptional trans-activator activity as well as the capacity to bind viral DNA replication factor E1 (Kajitani, Satsuka, Kawate, & Sakai, 2012). The E2 gene has four binding sites on the HPV-16 long control region (Kajitani et al., 2012). A binding site represents a potential attachment point that could be blocked by a drug, thereby preventing the completion of the HPV replication life cycle. Because E2 plays an intricate and important role in the replication life cycle of HPV, it is a potential target to be used with HTS for drug discovery.

In the normal cell cycle, uninfected basal cells in the epithelium exit the cell cycle soon after migrating to the suprabasal cell layers and undergo terminal differentiation (Doorbar, 2006). Cells in a terminally differentiated state are not mitotically active. Accordingly, the cell's DNA replication activity is suppressed in differentiated cells that exit from the cell division cycle (Kajitani et al., 2012). In order to sustain replication, HPV must reactivate the cell division process in differentiated cells. It does this with the expression of E6 and E7. E6 and E7 are the primary oncogenes in HPV and together they are responsible for dysplastic changes at the cellular level and the progression to invasive cancer. E6 and E7 function by

inactivating p53 and retinoblastoma protein (pRb; Matthews et al., 2003). The normal functions of p53 and pRb are to enable cells to maintain cell cycle DNA potential (Munger et al., 2004). Through the transcription process, E6 and E7 prevent the normal function of p53 and pRb, thus allowing the cell to support HPV DNA replication (Doorbar, 2006). This suggests that the expression of E6 and E7 are predisposing factors in the development of HPV-associated cancer (Doorbar, 2006). The ability of E6 and E7 to commandeer the cell's natural cell life cycle makes these oncogenes ideal targets for drug discovery. A drug that could interrupt E6 and E7 inactivation of p53 or pRb would have great therapeutic value to prevent HPV-related infections.

In addition to gene expression, proteins have the potential to make ideal biologic targets because they tend to be associated with antibody expression. HPV encodes two structural proteins, L2 and L1, which are expressed in the upper layers of infected tissue (Doorbar, 2006; Joyce et al., 1999, Middleton et al., 2003). L1 and L2 have evolved to fulfill multiple roles that are critical to establishing HPV infection. L2 is often characterized as a good candidate for prophylactic vaccine development because L2-specific antibodies have cross-neutralizing activity against diverse HPV types (Schiller, Day, & Kines, 2010). For nonenveloped viruses, such as HPV, the protein coat encases and protects viral nucleic acid as well as provides the initial interaction site of the viral particle with the host cell (Horvath, Boulet, Renoux, Delvenne, & Bogers, 2010). This allows assembly of infectious HPV particles in the upper layers of the epithelium (Doorbar, 2006; Roden et al., 2001), which is why L2 was chosen as the biologic target for the development of the HPV vaccine (Merck and Co., Inc., 2014).

HPV Pathogenesis and Progression

This section ties together the pathogenesis of HPV and its progression to cancer. HPV forms high-grade lesions at sites where the productive life cycle cannot be completed, and this process is referred to as an abortive infection. High-grade lesions have a more extensive proliferative phase than normal cells and the productive stages of the viral life cycle are either not supported or supported only poorly (Burk, Chen, & Van Doorslaerb, 2009; Doorbar, 2006). The key event in the progression of productive lesions to aHSIL may result from a deregulation of the expression of the E6 and E7 proteins (Middleton et al., 2003). Decreased expression of these two viral transforming proteins leads to increased cell proliferation in the lower epithelial layers and an inability to repair mutations in the host cell's DNA (Doorbar, 2006).

The transformation zone or squamous-columnar junction is a particularly susceptible site for anal cancer to develop. A predominate theory is that high-risk HPV types such as HPV-16 cannot reliably complete the life cycle at this site, which occasionally leads to abortive infections (Doorbar, 2006). Progression from high-grade aHSIL to cancer usually occurs in lesions that contain integrated copies of viral genome in which E7 expression is elevated (Doorbar, 2006). This again highlights the need for HIV nurse clinical scientists to recognize HPV-related disease burden in PLWH and to identify novel interventions to prevent high-risk groups and the general population from developing anal cancer and HPV-related

infections. HTS plays a critical role in the discovery of compounds able to prevent HPV infection.

HTS is an important step in the discovery of new therapeutic modalities. The primary advantage to HTS is that it allows a researcher to quickly scan thousands of compounds in a compound library. The automated process uses liquid handling and robotic arms to inject small volumes of drugs or molecules into 384-well plates in several hours. Through this process, one can rapidly identify active compounds that modulate a particular HPV biomolecular pathway (Huang et al., 2012). The alternative method involves manual pipetting of each compound into an individual well on a 384-well plate. This labor-intensive method would render drug discovery nearly impossible. In addition to the physical labor required, a high degree of error occurs when a researcher pipettes less than 1 μL. However, HTS does have several drawbacks: it is expensive, results are generalizable only to the library screened, and few studies have used HTS to identify novel compounds capable of inactivating or inhibiting HPV viral entry (Buck et al., 2006; Huang et al., 2012).

High-Throughput Screening for HPV Drug Discovery

The use of HTS in the field of virology is a relatively new idea. One reason for this may be that HTS is dependent on a biologic target to identify drugs. Viruses are complex living organisms that interact with host cells to establish infection. The biology underlying the infectious process must be defined and quantified first, which may take years to fully comprehend. The contributions of HPV biologists to the field of virology have made it possible to identify biologic targets within HPV (i.e., L2 and E2) to be used with HTS for drug discovery. Currently, only two articles have reported on the use of HTS for HPV drug discovery (Buck et al., 2006; Huang et al., 2012).

Buck and colleagues (2006) developed an inhibition assay by optimizing a pseudovirions (PsV) plasmid expressing the biologic targets of L1 and L2. PsV are noninfectious HPV plasmids that can be created to express L1 and L2. The PsVacts as a segregate maker for HPV infection. The inhibition assay was developed to perform HTS in a library of several thousand compounds to identify hits or compounds able to prevent HPV infection. The assay used flow cytometric analysis to assess the inhibition of PsV-mediated delivery of a green fluorescent protein reporter plasmid into HeLa cells. Any compound that prevented the green fluorescent protein expression was identified as a hit (i.e., compounds able to prevent PsV from entering the cell and preventing infections). Buck and colleagues (2006) identified carrageenan, a type of sulfated polysaccharide extracted from red algae, as an extremely potent infection inhibitor for a broad range of sexually transmitted HPVs.

Recently, HTS assay was used to identify two additional compounds able to inhibit HPV infection (Huang et al., 2012). A cell-based HTS assay was developed using HPV16 PsV plasmid expressing L2. Huang and colleagues (2012) screened a compound library of 40,000 elements consisting of commercially available bioactives, U.S. Food and Drug Administration-approved drugs, natural organics, and predesigned drug-like small molecules. Two lead compounds were chosen for further analyses based on the structure-activity relationship (e.g., relationship between the chemical of a molecule and its biologic activity), scaffold diversity, strength of the inhibitory activity, and low cytotoxicity. The

compounds, identified as #13 and #14 by the authors, showed low to submicromolar inhibitory concentration (IC_{50}) and little to no cytotoxicity. IC_{50} is the half maximal inhibitory concentration that is a measure of the effectiveness of a compound in inhibiting biologic or biochemical function. This can be interpreted as compounds #13 and #14 at their optimal micromolar (μM) concentration prevented 50% of PsV inhibition while exhibiting little to no cell toxicity. Preliminary results suggested that compounds #13 and #14 could inhibit multiple genital HPV types (Huang et al., 2012). The road to bringing a novel drug or compound to the clinical setting is long and arduous; the initial discovery is only the first step. Although the results from Huang and colleagues (2012) seem promising, they will need to be biologically reproduced; additional experiments to identify mechanism of action for #13 and #14 need to be performed. This process can take years.

Other High-Throughput Screening Drug Discovery

A number of studies have used HTS assays to identify compounds able to prevent viral infections other than HPV, including filoviruses (Basu et al., 2011), HIV (Marin et al., 2015), and Epstein-Barr virus (Thompson, Messick, Schultz, Reichman, & Leiberman, 2010). Additionally, HTS has been used effectively to screen and identify potential anti-metastatic drugs (Mahida et al., 2013) for cancer, and for anti-inflammatory disorders (Kumar et al., 2011).

Summary

The Results section emphasized the complex and intricate events in the life cycle of HPV, pathogenesis to aHSIL, and use of HTS for drug discovery. Several naturally occurring events in the HPV life cycle have the potential to be developed into biologic targets for HPV HTS including: (a) E2, (b) E6 and E7, (c) L1, and (d) L2. The HPV life cycle helps to keep developing infections under the radar of the human body's robust immune system. Upon infection, HPV does not present with typical signs and symptoms (i.e., pain, fever, or cough). This adds to the barriers of introducing population-level interventions to reduce the risk of HPV infections. This highlights the need for HIV nurse clinical scientists to investigate and understand HPV biology and pathogenesis at the cellular and molecular levels in order to develop potential biologic targets into HTS assays to discover new compounds that may be developed into treatment interventions. Novel treatment interventions help high-risk individuals such as PLWH and HIV-infected MSM reduce exposure to HPV-related infections and cancer.

Discussion

HIV nurse clinical scientists are on the forefront of molecular health research focused on evaluating the relationships between the HIV-infected patients' continua of health care and prevention of opportunistic oncogenic HPV infections (Palefsky et al., 2012; Rudy & Grady, 2004). HPV-related infections have the potential to cause precancerous lesions in the anal canal that may progress to anal cancer. Although most people will be exposed to HPV in their sexual lifetimes, certain high-risk groups, including PLWH and MSM, are at increased risk for developing HPV-related anal cancer (Glick et al., 2014). The current prevention options for sexually active people are limited. However, through the use of HTS for drug

discovery, several compounds with the potential to inhibit HPV infection have been identified. It remains worthwhile to mine additional compound libraries to identify novel compounds able to prevent HPV infections. The identification of these compounds creates an opportunity to develop prevention interventions such as a personal lubricant or mouth-wash that can be administered before intercourse as an intervention to help protect all people from HPV-related infections and the development of pre-cancerous lesions.

HIV nurse clinical scientists are in a unique position to translate basic science into viable clinical applications. Nursing science addresses the individual from a multidimensional perspective, and the questions they generate from clinical settings are often grounded in basic biology. The ability to combine clinical and translational research enables nurse clinical scientists to directly contribute to the patient's continuum of care. Additionally, nurse clinical scientists have the potential to contribute to a diverse body of basic science knowledge from a perspective driven from the nursing scope of practice.

There are several limitations to this review of the literature. HTS is a well-established technique used in pharmaceutical industries for small molecule and drug discovery. HTS is a relatively new method being used in the field of virology for drug discovery, and at this time there are few published articles to validate the process (Basu et al., 2011; Buck et al., 2006; Huang et al., 2012). Additionally, few published articles using HTS for HPV drug discovery limit biologic reproducibility, making it hard to directly compare results (Buck et al., 2006; Huang et al., 2012). In general, it is difficult to directly compare studies because information on assay development, composition of compound libraries, and z-prime parameters are limited in the literature or not provided. There is also a lack of contributions from the clinical nursing perspective by nurse clinical scientists. The patient care component of a nurse's body of knowledge is incredibly powerful, and nurse-scientists have the potential to develop future research questions guided by clinical insight. HIV nurse clinical scientists have the capability to integrate basic science with patient-centered care, and intimate knowledge of HPV biology and patient care is a major asset. Its contribution may help to inform future development of new therapeutic methods.

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Key Considerations

- Collective efforts will allow HIV nurse clinical scientists to provide care and advise patients on treatment options.
- Knowledge gained from research will fuel additional efforts in the development of HPV prophylactic interventions for all sexually active individuals.
- Translating research into clinical practice will provide more robust prevention methods for sexually active individuals, specifically, people living with HIV and HIV-infected men who have sex with men, to reduce the risk of exposure to HPV-related infections, anal high-grade squamous intraepithelial lesions, and anal cancer.

Table 1.

Review of the Literature

Type	Database	# Articles Retained
Literature search	PubMed	23
	CINAHL	5
References		
HPV biology and pathogenesis	Burk et al., 2009; Da Costa et al., 2002; Day & Schelhaas, 2014; Doorbar, 2006; Duncan et al., 2015; Guiguet et al., 2009; Hessol et al., 2009; Joyce et al., 1999; Kajitani et al., 2012; Machalek et al., 2012; Matthews et al., 2003; Middleton et al., 2003; Morshed et al., 2014; Munger et al., 2004; Pokomandy et al., 2011; Pyeon et al., 2009; Roden et al., 2001; Schiller et al., 2010; Stanley et al., 2012; Strickler et al., 2005; Uronis & Bendell, 2007	
Use of HTS for drug discovery	Basu et al., 2011; Buck et al., 2006; Huang et al., 2012; Kumar et al., 2011; Mahida et al., 2013; Marin et al., 2015; Thompson et al., 2010	

Note. HPV = human papilloma virus; HTS = high-throughput screening techniques.