The epidemiology of human papillomavirus in HIV-negative and HIV-infected men who have sex with men
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Chapter 1

Introduction
Introduction

HPV – a brief history
In the early 1970s a link between human papillomavirus (HPV) and cervical cancer in women was postulated by Harald zur Hausen [1]. In the following decades, his discovery proved to be of major importance and was rewarded with the Nobel Prize in 2008 [2]. HPV was not only identified as the cause of cervical cancer, but was associated with other anogenital cancers, head and neck cancers, and cutaneous cancers in both women and men [3]. To date, it is estimated that 4.8% of all cancers worldwide are attributable to HPV [4].

HPV – biology
More than 150 HPV types are currently known to infect humans [5;6], with a large diversity in tissue tropism, viral life-cycle, and symptomatology. These HPV types are divided into 5 genera based on their DNA sequence [5;7]. All mucosal HPV types, which are most relevant in causing HPV-related cancers, belong to the alpha-genus [8].
Mucosal HPV types can be categorized into high-risk (group 1) and low-risk types (groups 2A, 2B, and 3), based on their oncogenic potential for cervical cancer [3]. Low-risk HPV types, for example HPV-6 and -11, are associated with anogenital warts and mild dysplasia, but are rarely found in high-grade lesions. Persistent (i.e., long-standing) infection with a high-risk HPV type, notably HPV-16 and -18, is associated with high-grade dysplasia and cancer [8].
HPV infects the basal layers of the epithelium via micro-abrasions or wounding [9]. Once a productive infection is established, the basal cells form a reservoir of infection, in which the viral genome is maintained at low-copy numbers, and viral particles are shed at the epithelial surface [8;9]. Despite several strategies to evade the host’s immune system [10], around 90% of HPV infections are cleared by the immune system within 2 years [11;12].

HPV – epidemiology
HPV is the most common sexually transmitted pathogen worldwide [13]. HPV infections are highly transmissible, and the vast majority remains asymptomatic or subclinical. Both host characteristics (e.g., sexual behavior, immunological factors like HIV infection, smoking, concurrent sexually transmitted infections (STI), and circumcision status) and viral characteristics (e.g., viral load) play a role in the transmission of HPV [10].
The lifetime risk of acquiring an HPV infection in sexually active individuals is estimated to be 80% [14], and the risk is particularly high soon after sexual debut. In women, peak prevalence is observed at young adult ages (less than 25 years), although in some regions of the world a small second peak can be observed in middle-aged women [4]. In men, less is known, but the available data indicate that HPV prevalence in men is more constant throughout life [15]. Prevalence of anogenital HPV infection in men varies widely across studies, with estimates between 1 and 84% in men without increased risk of HPV infection [16,17]. This wide range of observed prevalence among men may be explained by differences in study populations, sampling methods (including the anatomical sites of sampling), and laboratory methods used. Prevalence of anal HPV infection in men who have sex with men (MSM) is higher than in men who have sex with women (MSW) [18], with highest estimates of up to 93% among HIV-infected MSM [16]. Oral HPV prevalence is generally much lower, around 4.5% in healthy individuals [19], but recent studies indicate that oral HPV prevalence among HIV-infected MSM may range between 20 and 45% [20].

**Knowledge gaps in HPV epidemiology**

In recent years, a growing body of literature reports on the burden of HPV infections in men, after the primary focus had been on cervical HPV infection in women. However, there are important knowledge gaps regarding the epidemiology of HPV infection in men, particularly regarding MSM, who are at increased risk of HPV infection. There is a lack of insight in 1) the anal, penile, and oral HPV prevalence, incidence, and clearance among HIV-negative and HIV-infected MSM, and 2) determinants for anal, penile, and oral HPV prevalence, incidence, and clearance among HIV-negative and HIV-infected MSM.

**HPV – immunology**

Previous studies suggested that around 40-60% of women, and probably a lower proportion of men, produce HPV type-specific antibodies upon infection [21-25]. As naturally induced HPV antibodies may persist for many years or decades [21,26], seropositivity can be regarded as a marker of previous HPV exposure. A Dutch population-based study showed that around 25% of females and 20% of males between 14 and 79 years of age were seropositive for one or more of seven high-risk HPV types [27].
Knowledge gaps in HPV immunology
Clearance of HPV infection is probably mediated by the cellular immune system [28]; the role of the humoral immune system is less well understood [25;29]. There is limited knowledge on HPV serology in men, particularly regarding the associations between HPV infection and HPV antibodies. It has been hypothesized that HPV infections in mucosal epithelium (e.g., anal infections) are more likely to induce a humoral immune response than infections in keratinized epithelium (e.g., infections of the penile shaft) [30-32]. Moreover, it is unclear whether naturally induced HPV antibodies confer protection against incident HPV infection; this is in contrast to the protective effect that has been related to the much higher antibody concentrations observed after prophylactic HPV vaccination [33;34].

HPV–related cancer in men

Anal cancer
More than 80% of anal cancer is associated with HPV, most frequently HPV-16 [35]. Anal cancer is relatively uncommon in the general population [36], but a high incidence has been reported among MSM, and especially among HIV-infected MSM [37]. In the era of combination antiretroviral therapy (cART), incidence of anal cancer has increased among HIV-infected individuals, in contrast to the AIDS-defining malignancies which showed a sharp decline [38]. The incidence of anal cancer in HIV-infected MSM is now even higher than the incidence of cervical cancer in unscreened female populations [37;39]. Like in cervical cancer, progression from normal mucosa to anal cancer occurs through several precancerous stages, named anal intra-epithelial neoplasia (AIN) 1 to 3. AIN1 is considered low grade AIN (LGAIN); AIN 2 and 3 are considered high-grade AIN (HGAIN). AIN of any grade is present in more than half of HIV-infected MSM, and around half of these lesions are HGAIN [37;40]. Only part of the precancerous lesions will eventually lead to cancer, but data on progression from AIN to anal cancer are limited. A recent longitudinal study found that nearly one quarter of HGAIN lesions regresses spontaneously within one year, while a minority of HGAIN (around 1% per year) progresses into anal cancer [41]. Unlike for cervical cancer, there are no standard screening tools for prevention of anal cancer at present. Anal cytology is controversial due to its low specificity
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[42]; HPV testing of anal swabs seems unsuitable due to the high anal HPV prevalence in high-risk groups and the lack of concordance with lesion-specific HPV types [43]. Thus, alternative screening options are now the subject of international debate. High resolution anoscopy (HRA) with biopsies of suspect lesions is considered the gold standard for detection of AIN in high-risk groups, although there are several important challenges: HRA is costly, requires a long learning curve, is unpleasant for the patient, the optimal treatment for HGAIN has not yet been established, and recurrence of HGAIN after treatment is relatively high [44;45].

Penile cancer
Penile cancer is a relatively rare malignancy [46], with a moderately increased incidence among HIV-infected men [47;48]. Around 45% of penile cancer is associated with HPV, most frequently types 16 or 18 [49].

Head and neck cancer
Head and neck squamous cell carcinoma (HNSCC) is the 6th most common cancer worldwide [50], and includes cancers of the oropharynx, oral cavity, and larynx. While smoking and alcohol use were traditionally the main risk factors, in recent years it has become clear that HPV, predominantly HPV-16, also plays an important etiologic role in subsets of HNSCC [3]. HPV prevalence in HNSCC varies widely by geographical region and anatomical location, with highest prevalence of up to 36-72% in oropharyngeal squamous cell carcinomas [51;52]. HPV-related HNSCC is now considered a distinct entity with a more favorable prognosis [53]. Although the incidence of smoking- and alcohol-related HNSCC seems to decrease over the past decades in the developed world, the incidence of HPV-related HNSCC is increasing in many parts of the world [52;54;55]. Similar to other HPV-related cancers, HIV-infected individuals have shown to be at increased risk of HPV-related HNSCC [47;48].

HPV vaccination
Two prophylactic HPV vaccines are currently on the market, primarily developed to prevent cervical cancer in women: a bivalent vaccine (Cervarix®) targeting HPV-16 and -18, and a quadrivalent vaccine (Gardasil®) targeting HPV-16, -18, -6, and -11. Both vaccines have shown to be highly effective in preventing new HPV infections and precancerous lesions associated with these HPV types [34].
In many countries throughout the world young girls are offered vaccination free of charge, as vaccination at young age (prior to sexual debut) is expected to prevent 70% of cervical cancers [56;57]. In the Netherlands, vaccination of girls in the year that they become 13 years of age was included in the national vaccination program in 2009.

There is ongoing international debate about whether boys should also be vaccinated. In 2011, a study showed that the quadrivalent vaccine was effective in preventing anal HPV infection and anal precancerous lesions in young MSM with 5 or fewer lifetime sexual partners [58]. Based on these data, the Advisory Committee on Immunization Practices (ACIP) in the USA recommended routine use of the quadrivalent vaccine in boys aged 11 or 12 years. Most other countries (including the Netherlands) have not yet implemented routine HPV vaccination for boys, for several reasons: the protection against actual anal cancer (and potentially other HPV-related cancers, for example HNSCC) has not been demonstrated, the duration of protection is unknown, and most cost-effectiveness analyses indicate that it is not cost-effective to vaccinate boys [59].

**HIV infection**

HIV infection can be transmitted through unprotected sexual intercourse, blood-blood contact, or during and after birth. Globally, an estimated 35.3 million people were HIV-infected in 2012, the majority of them living in Sub-Saharan Africa [60]. In the Netherlands, over 16,000 HIV-infected patients were registered in 2012. The majority of the annual number of new cases in the Netherlands (approximately 700-750 out of 1100) is among MSM [61].

HIV causes immunodeficiency by primarily targeting CD4 T-cells, which are a pivotal part of the adaptive cellular immune system, and normally coordinate pathogen-specific immune responses. By doing so, the virus replicates itself while impairing the system that would normally attack the virus. Moreover, HIV has several mechanisms to escape the host’s immune system, so that the immune system is unable to produce an effective immune response and eliminate the virus. As immunodeficiency increases, other (opportunistic) infections get a chance to infect and cause disease.

**Knowledge gaps in the role of HIV infection in HPV infection**

Although HIV-infected individuals are known to be at increased risk of HPV infection and HPV-related diseases, it is unclear whether this increased risk is
due to shared routes of transmission or to HIV-related immunosuppression. There are data suggesting a direct biological effect of HIV infection on HPV natural history, independent of sexual behavior. For example, two large studies among sexually inactive women have shown higher rates of new HPV detection in HIV-infected compared to HIV-negative women, whereby the detection rate increased with increasing immune suppression [62,63]. These observations indirectly support the hypothesis of reactivation of latent HPV infection (i.e., a state of immunological control of infection below detection thresholds of HPV assays), which may be more common among persons with HIV-related immunosuppression [29]. Moreover, data suggest that HIV-infected individuals are less capable to clear an HPV infection, resulting in higher HPV prevalence and persistence [10].

**HIV & HPV in MSM (H2M) study**

A prospective cohort study among MSM was started in 2010 in Amsterdam, the Netherlands, which was a collaboration between the Public Health Service (GGD) Amsterdam, the National Institute for Public Health and the Environment (RIVM), Jan van Goyen Medical Center (MC Jan van Goyen), Academic Medical Center (AMC), and Vrije Universiteit-University Medical Center (VUmc): the HIV & HPV in MSM (H2M) study.

In total, nearly 800 HIV-negative and HIV-infected MSM were recruited. Participants were followed-up every 3 to 6 months during 24 months per participant. At each visit, participants completed self-administered questionnaires and collected anal, penile, and oral self-samples for HPV DNA analyses. Serum samples were taken for HPV serology. In addition, STI screening was performed. After 2 years of follow-up, participants were informed about their personal anal and penile HPV status. In case of a persistent anal high-risk HPV infection in an HIV-infected participant, the participant was advised to undergo HRA in one of the 4 HIV treatment centers in Amsterdam currently performing HRA.

**Aims and outline of this thesis**

This thesis aims to assess the epidemiology of HPV in HIV-negative and HIV-infected MSM. The knowledge gaps in the introduction above refer to the main research questions of the H2M study. These questions are the following:
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- What are the type-specific HPV prevalence, incidence, and clearance of anal, penile, and oral HPV infections among HIV-negative and HIV-infected MSM? What are determinants for anal, penile, and oral HPV infection?
- What is the type-specific HPV seropositivity among HIV-negative and HIV-infected MSM? What are determinants for seropositivity?
- What is the concordance between HPV infections at various anatomical sites and HPV seropositivity?
- Do HPV infections lead to type-specific seroconversion?
- Do naturally induced HPV antibodies confer protection against incident type-specific anal or penile HPV infection?

In this thesis these questions are addressed by analyses and interpretation of data collected in the H2M study.

**Part 1** starts with a review on HPV and anal cancer in HIV-infected individuals. The following chapters report the anal and penile HPV prevalence, incidence, and clearance. The independent association between HIV and HPV is assessed, as well as other determinants for anal and penile HPV infection in HIV-negative and HIV-infected MSM.

**Part 2** reports on oral high-risk HPV infection in MSM. Again, the role of HIV infection in oral HPV prevalence, incidence, and clearance is assessed, as well as other determinants for oral HPV infection. In addition, it describes which HPV types -apart from the known mucosal types- can be detected in the oral cavity.

**Part 3** reports the HPV seropositivity in MSM, and the association between HIV infection and HPV seropositivity. Furthermore, it analyses the concordance between HPV infections at various anatomical sites and seropositivity. Also, it investigates HPV seroconversion following anal and penile HPV infection, and whether naturally induced HPV antibodies confer protection against subsequent type-specific HPV infection.

**Part 4** provides a summarizing discussion, in which the main findings of this thesis are elaborated and future perspectives are given regarding research and public health.
References

Chapter 1


