Anal intraepithelial neoplasia in HIV+ men
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Chapter 1

Introduction
Since the introduction of combination antiretroviral therapy (cART), the incidence of AIDS-defining infections and malignancies in HIV-infected patients has decreased markedly, whereas the incidence of certain non-AIDS-defining malignancies has increased. The increased life expectancy, the reduction of competing causes of death and increased rates of high-risk behaviors, such as tobacco use, might contribute to the increased incidence of these non–AIDS-related malignancies. The largest increase in incidence is seen for anal cancer. While in the general population anal cancer is a rare disease with incidence rates between 0.5 and 2 per 100,000 person-years, in HIV patients the incidence has increased from 11-40 in the pre-cART era up to 40-80 in the cART era. Although an increase is seen in all HIV subgroups, the highest incidence by far is seen in HIV+ men who have sex with men (MSM), with incidence rates between 65 and 144 per 100,000 person-years in the cART era.

Like cervical cancer, human papillomavirus (HPV) is the main etiologic factor of anal cancer, and progression from healthy mucosa to anal cancer occurs likewise through several precancerous stages. In analogy with cervical intraepithelial neoplasia (CIN), the anal precursor is called anal intraepithelial neoplasia (AIN), and AIN commonly occurs at the anal transformation zone, where the squamous epithelium of the anal canal transitions in the columnar epithelium of the distal rectum. Depending on the extent of spread of the dysplastic cells within the epithelial layer, AIN is graded from 1 to 3. More and more AIN 1 is referred to as low grade (LG) AIN and AIN2/3 as high grade (HG) AIN.

The gold standard in AIN diagnostics is histopathological evaluation of suspect lesions visualized via high resolution anoscopy (HRA). Anal cytology does not seem to be useful for the screening of AIN. It underestimates the presence of HGAIN and the specificity is low. Unfortunately, HRA is time-consuming and cumbersome for the patient.

It is assumed that only a minority of (HG)AIN undergoes malignant transformation to anal cancer. However, data on progression are very limited. Two small studies show rates of progression in HIV+ MSM of around 15% during median follow-up periods of 2 and 5 years. A recent review calculated a theoretical progression rate per year of 1 in 377 in the cART era. By way of comparison, inadequately treated CIN 3 progresses to cervical cancer in 30% of patients over a period of 30 years.
AIN is present in 50-80% of HIV+ MSM. About half of these lesions are HGAIN. Given the similarities with CIN, AIN-screening and –treatment might be useful to prevent anal cancer. Unfortunately, this has only recently attracted the attention of the medical community, and many issues regarding AIN diagnostics, screening strategies and treatment are at present unresolved.

In this thesis we approached this subject on four levels: Epidemiology of anal cancer (part I), Risk factors and diagnostics of AIN (part II), Treatment of AIN (part III) and Pathophysiology of anal HPV infection (part IV).

**Part I: Epidemiology**

The anal cancer incidence has been increasing in the general population in Western countries in the last two decades. Chapter 2 is a review of the literature on anal cancer incidence in Western countries. We tried to explain the grounds of this increasing incidence by identifying known risk factors and risk groups of anal cancer. The focus is on changes in anal cancer incidence among these risk groups, to see whether such changes, if present, could explain the overall increase in anal cancer incidence. Despite the use of cART, the anal cancer incidence in HIV+ men continues to increase. In Chapter 3 we explored the incidence of anal cancer in the Dutch HIV+ population in the cART era, and we analyzed a range of potential risk factors in relation to anal cancer.

**Part II: Diagnostics**

Screening for AIN requires a proper screening method. HRA is time-consuming and cumbersome for the patient, and in addition, there is a lack of HRA-experienced physicians and nurses. Identification of risk factors could be a way to pre-select a population at higher risk for AIN. Chapter 4 is a cross sectional clinical study in which we investigated a wide range of potential risk factors for AIN in 311 HIV+ MSM, with HRA as primary screening tool. Our goal was to establish factors that might help to identify HIV+ MSM at greatest risk for having AIN.
Currently, only a limited number of physicians are experienced in HRA, and training programs should be implemented to facilitate future AIN screening. However, HRA is a complicated procedure, and a systematic comparison between clinical features and the histopathology of suspect lesions is lacking. In Chapter 5 we analyzed interobserver agreement in classifying features of intra-anal lesions suspect for AIN and compared these features with their histopathological outcome. HRA anoscopyists need extensive training and they have a long learning curve.18 However, to date no studies have been conducted to quantify this learning curve. Chapter 6 reports on the HRA-learning curve of the author of this thesis, by analysing AIN prevalence with increasing experience.

Part III: Treatment

Screening for a disease is only sensible if effective treatment is available. So far, no treatment guidelines exist. Current treatment options have low to moderate response rates and the majority of lesions recurs. In addition, most studies are retrospective and only a few small prospective studies have been performed.19-23 Previous studies have shown that topical 5-FU is effective in several anogenital premalignant intraepithelial lesions, such as CIN, vaginal intraepithelial neoplasia (VAIN) and penile intraepithelial neoplasia (PIN).24-26 Given the biological similarities between these entities and AIN, we hypothesized that 5-FU might be beneficial in AIN. In Chapter 7 we report a multicentre single-arm trial evaluating the efficacy and safety of topical 5-fluorouracil for the treatment of intra-anal AIN. In previous (retrospective) studies electrocautery and infrared cautery seem to be the best treatment options.21,22 Topical treatments might be a good alternative, given the fact that patients can treat themselves at home. Moreover, electrocautery has side effects, like anal stenosis, incontinence, scarring and disfiguration. In Chapter 8 we report a randomized triple-arm trial in 148 HIV+ MSM comparing the efficacy and side effects of topical 5-fluorouracil, imiquimod and electrocautery for the treatment of AIN.
Part IV: Pathophysiology

Knowing which HPV types cause disease is essential for vaccination programs and understanding the aetiology of AIN. In addition, identification of the causative HPV type might help to predict the malignant potential of an AIN lesion. In the vast majority of HIV+ MSM anal swabs contain multiple HPV types, and AIN whole tissue sections (WTS) also often contain multiple HPV types. The question is which of these HPV types is causing the lesion and which are innocent bystanders. Laser-capture micro-dissection (LCM) combined with sensitive and type-specific PCR has proven to be a reliable method to identify the lesion-specific HPV genotype in cervical and vulvar (VIN) intraepithelial neoplasia.

In Chapter 9 we investigated the hypothesis that individual components of HGAIN lesions are associated with one single HPV type. Secondary goals were to survey the spectrum of HPV types responsible for HGAIN in HIV+ MSM and to compare HPV types found in swabs, WTS and LCM-selected regions.

Interaction between HIV and other viral pathogens might influence viral dynamics in both directions. It has been shown that HIV-1 positive individuals are less prone to clear their HPV infection compared to uninfected individuals. In addition, higher HIV-1 viral shedding was reported among both men and women co-infected with HPV. Prolonged HPV infection of the anal mucosa will result in inflammation that will undoubtedly increase the numbers of immune cells both carrying HIV-1 as well as uninfected cells with heightened susceptibility for infection. In Chapter 10 the hypothesis that HPV infection can influence the HIV-1 load in anal mucosa is addressed, by comparing HIV-DNA and –RNA levels in HGAIN lesions and in adjacent normal anal mucosa.

In the Chapter 11 we summarize the main results and implications of this thesis and discuss recommendations for future research.
Chapter 1

References


