Anal intraepithelial neoplasia in HIV+ men
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Chapter 11

Summary and Discussion
In this thesis we investigated several aspects of anal intraepithelial neoplasia (AIN) in HIV+ men who have sex with men (MSM). This condition has gained clinical interest because of the impressive increase of the anal cancer incidence in HIV+ MSM since the introduction of combination antiretroviral therapy (cART). The incidence of anal cancer among HIV+ MSM is now much higher than the incidence of cervical cancer in HIV- negative women before standard cytological screening was introduced, and given the similarities between anal and cervical cancer, screening for and treatment of AIN to prevent anal cancer is presently subject of debate.

Part I: Epidemiology

In Chapter 2 we found that during the last decades the incidence of anal cancer has increased in the general population of most Western countries. Infection with oncogenic human papillomavirus (HPV) is the most important risk factor, but anal cancer is also associated with increasing age, smoking, receptive anal intercourse, a history of sexually transmitted infections, having had more than 15 lifetime sexual partners, and a history of cervical intraepithelial neoplasia or cervical cancer. The main risk groups are HIV positive patients, men who have sex with men, and organ transplant recipients. Increasing numbers of people belonging to these risk groups contribute to the increase in anal cancer incidence. Further studies should answer in more detail to what extent these risk groups contribute to the overall anal cancer incidence, and whether these risk groups would benefit from preventive screening for anal cancer.

In Chapter 3 we describe that since the introduction of cART in 1996 the anal cancer incidence in the HIV positive population in The Netherlands has increased, to a peak incidence rate of 114 per 100,000 person-years in 2005/2006. In HIV+ MSM this peak incidence was even 168 per 100,000 person-years. However, after 2006 a steady decrease to an incidence of 72 and 100 per 100,000 person-years respectively was found. Main risk factors were a low nadir CD4 cell count, alcohol abuse and smoking.

This is the second study that shows that the incidence rates are levelling off. An explanation might be that long-term use of cART is negatively associated with the risk of the anal cancer precursor AIN and furthermore, given the tendency to start cART with higher CD4 counts, the HIV+ MSM population is less and less
exposed to low nadir CD4 cell counts. cART is initiated at higher levels in the last 10 years compared to the beginning of the cART era. In time, this might lead to a decrease in anal cancer incidence.

Our findings support early initiation of cART in all patients. In the coming years we will see whether the incidence of anal cancer in HIV+ MSM will continue to decrease. In the meantime, the very high anal cancer incidence justifies screening programs for AIN among HIV+ MSM.

**Part II: Diagnostics**

In Chapter 4 we found several risk factors for AIN in HIV+ MSM. GHB use increased the risk for AIN, while duration of cART and anal XTC use were negatively correlated with AIN. These parameters were combined into one multivariable predictor to select HIV+ MSM for AIN screening. To reach a negative predictive value of 100%, only 3% of the participating patients could be rightfully excluded from screening. In other words: no predictor or set of predictors that is useful to guide an AIN-screening program was found.

Chapter 5 showed that a moderate to substantial interobserver agreement can be reached between two experienced high resolution anoscopists in recognising anal lesions suspect for AIN in HIV+ MSM. Furthermore, HGAIN was present in almost 20% of anal condyloma, a presumed benign abnormality. Condylomatous lesions should therefore always be biopsied for histopathological evaluation in this high-risk group. In non-condylomatous lesions, a combination of punctuation, flat leukoplakia and atypical vessels was the best predictor for HGAIN.

In Chapter 6 we established a learning curve for high resolution anoscopy (HRA) for the first author. 383 HIV+ MSM (with identical inclusion criteria and selection procedures) were divided in 6 consecutive groups of 63 men. In the first group, an AIN prevalence of 40% was found. In the last two groups, the AIN prevalence levelled off at 70%, with a concomitant gradual decrease in AIN and HGAIN prevalence over time for the second screening in patients who were presumed AIN-negative at baseline. These data support and quantify the previously reported lengthy learning curve required for HRA practitioners.
Given the very high prevalence of (HG)AIN and the absence of a useful (set of) predictor(s), screening seems warranted for all HIV+ MSM. However, given the association of low nadir CD4 counts with anal cancer (chapter 3), it is reasonable to give priority to those with a low nadir CD4 cell count, especially in situations of limited screening capacity. Anal cytology does not seem to be useful for the screening of AIN. It underestimates the presence of HGAIN and its specificity is low.\(^3\)\(^,\)\(^8\) HRA is a complicated procedure, which requires extensive training and experience. Given the lack of other qualitative screening methods, HRA-training programs need to be extended to facilitate future AIN-screening programs.

Part III: Treatment

In 48 HIV+ MSM with intra-anal AIN we found after treatment with topical 5-fluorouracil (5-FU) a complete clearance rate of 39% (Chapter 7). In addition, 5-FU caused a decrease of the viral load of oncogenic HPV in both responding and non-responding patients.

Chapter 8 describes an RCT in 148 HIV+ MSM, who were treated for (HG)AIN with imiquimod, 5-FU or electrocautery. The number of patients with a complete response at 4 weeks following end of treatment was significantly lower for patients in the imiquimod and fluorouracil groups than for those treated with electrocautery. Additionally, side-effects were more serious and longer lasting in patients treated with imiquimod and fluorouracil than in patients treated with electrocautery. However, in 70% of responding patients in all three treatment arms AIN lesions recurred within 18 months after treatment.

Future studies should focus on new treatment modalities. The high recurrence rates are unsatisfying and will absorb the scarce HRA-capacity. To our knowledge, currently no new promising local treatment is under investigation. Possibly, therapeutic vaccination, inducing specific T-cell responses, might be an option. This has previously been shown to be effective for the treatment of VIN.\(^9\) There might also be a role for prophylactic vaccines. A recent retrospective study showed less recurrences of HGAIN in patients who received the quadrivalent HPV vaccine after successful treatment.\(^10\) Both strategies are currently under investigation in the Academic Medical Center of the University of Amsterdam.
Part IV: Pathophysiology

In Chapter 9 we performed HPV genotyping on Whole Tissue Sections (WTS) and Laser Capture Microscopic (LCM)-selected regions of 31 HGAIN lesions obtained in 21 HIV+ MSM. We were able to identify the single and presumably causative HPV types in all regions of the HGAIN lesions, although 2 LCM-selected samples consisted of 2 colliding lesions. We showed that analysis of WTS is not sufficient to determine the causative HPV type if multiple HPV types are present, and anal swabs often do not contain the causative HPV type. Finally, we found that approximately half of the lesions are not caused by the two oncogenic HPV types (16 and 18) targeted by current prophylactic vaccines.

The question rises whether, based on the lesional HPV type, a differentiation can be made in malignant potential of a HGAIN lesions. HPV analysis of WTS and LCM-selected regions in anal cancer specimens of HIV+ patients might help to answer this question. In addition, information on the HPV types that will finally lead to malignant progression is essential for evaluation of the possible role of therapeutic and prophylactic HPV vaccines.

In Chapter 10 we analysed HGAIN lesions and healthy mucosa of 3 HIV+ MSM for HIV-1 viral load. Despite a suppressed plasma viral load, increased levels of HIV-1 RNA were found in intra-anal HGAIN lesions as compared with the adjacent healthy mucosa. This provides further evidence that antiretroviral therapy may not be able to completely suppress HIV-1 replication and that this can occur even more so in AIN lesions where localized inflammation is likely ongoing. It is also possible that drug concentrations are lower in AIN lesions, resulting in residual HIV-1 replication.

Recommendations

In conclusion, anal cancer is a serious problem in HIV+ MSM. Given the similarities with cervical cancer, screening for AIN with subsequent treatment might avert development of anal cancer. As shown in this thesis, all HIV+ MSM are at risk, as there are no parameters that can help to identify MSM more or less at risk for AIN, although given the association of low nadir CD4 counts with anal cancer, it is reasonable to give priority to those with a low nadir CD4 cell count. High Resolution Anoscopy (HRA) is the preferable first line screening method, but the
optimal screening interval still needs to be established. Electrocautery is presently the preferred treatment, but future research should focus on new treatment modalities. The high recurrence rates are problematic and repeated visits and treatments are logistically difficult and cumbersome for the patient. The contribution of therapeutic and prophylactic vaccination should be explored.

In addition, more knowledge is needed on the malignant potential of AIN. Is LGAIN a real precursor of anal cancer, or should the focus be on HGAIN? Can knowledge of the causing HPV type guide treatment decisions? Natural progression studies of HGAIN are needed, in combination with qualitative HPV analysis.

In the meantime, current available data plead for further introduction of AIN-screening programs. This means that HRA training programs need to be expanded.
References


