



## Anal cancer prevention: how we are failing men who have sex with men

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# Anal cancer prevention: how we are failing men who have sex with men

Ross D Cranston

Although receptive anal intercourse (RAI) is far from the sole preserve of men who have sex with men (MSM), the medical consequences of this sexual behaviour and resulting infection with human papillomavirus (HPV) are becoming increasingly apparent in this population. It is over 25 years since Daling *et al* reported on the increased rates of anal cancer in never married men with positive syphilis serology—their proxy for MSM.<sup>1</sup> These rates of up to 35:100 000 were similar to those of cervical cancer before the institution of routine cervical cytology screening, and much greater than the rate of 2:100 000 seen currently in the general population. Since then, MSM have borne the brunt of the HIV epidemic in Western society and, paradoxically, with the now widespread availability and impact of highly active antiretroviral therapy, we are now seeing rates of anal cancer in HIV positive MSM that are more than double those initially reported.<sup>2</sup> In contrast to other AIDS-associated malignancies, such as Kaposi's sarcoma, anal cancer rates continue to increase, a fact that clinicians, MSM and the HIV community at large seem, for the most part, unable or unwilling to address.

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## THE ANAL CANAL

The anal canal is 3–4 cm long and is lined with stratified squamous non-keratinising epithelium. It extends from the anal verge to the anorectal transition zone where it meets the unicellular columnar epithelium of the rectum. For the most part, it is only the anal canal and not the rectum that becomes infected with HPV.

## HPV

In the general population, anogenital HPV is the most common viral sexually transmitted infection. Supporting data from serological studies indicate that over 50% of sexually active North Americans have antibodies indicative of previous exposure to anogenital HPV.<sup>3</sup> HPV is both highly infectious and easily transmitted as demonstrated in a recent study showing an almost 30% risk of HPV acquisition in women from their first sexual partnership.<sup>4</sup> Despite this high prevalence, the natural history of HPV in women is for the most part benign. Most cervical HPV infections are asymptomatic with no clinical sequelae and are transient with the infection either “cleared” or becoming undetectable in over 90% of cases after 2 years.<sup>5</sup>

Since 2003, a test that allows real time diagnosis of HPV infection in women has been approved by the US Food and Drug Administration (FDA). This test uses

hybrid capture technology to differentiate 18 HPV types that infect the anogenital region into high risk or low risk groups.<sup>6</sup> Risk phenotype refers to previously established associations of HPV type with cervical cancer. This also translates to the association of HPV type to cancer risk at other anogenital sites in women, such as the vagina, vulva and anal canal—just as it does in men for cancer of the penis and anal canal.

## HPV INFECTION IN MEN

There is no FDA approved HPV test for men. This may be explained in part due to issues related to sampling technique and sampling site. For example, which site should be sampled when HPV infects glans, foreskin (if present) and shaft of the penis as well as the scrotum and perineum? HPV testing of the anal canal, in contrast to the penis, is a relatively straightforward procedure. Most anal HPV testing has been performed in a research context using PCR techniques that identify individual HPV types. Using this method it is apparent that MSM carry a high burden of HPV infection. The EXPLORE HPV sub-study of approximately 1200 HIV negative MSM in four North American cities showed that HPV is detectable in between 50 and 60% of men through a wide age range of 24–60 years, with rates of high risk HPV in the range of 20–30%.<sup>7</sup> It is clear from the cervical literature that persistence of high risk HPV is a risk factor for progression to high-grade dysplasia and cancer; finding a high and persistent level of high risk HPV in the anal canal may be a critical contribution to unravelling why MSM are at such high risk of anal cancer. Furthermore, in HIV positive MSM, HPV infection is an almost ubiquitous finding

with studies reporting prevalence rates upwards of 90%.<sup>8</sup> These men are also more likely to have higher concentrations of high risk HPV measured using semi-quantitative methods and are more commonly infected with multiple HPV types—both independent risk factors for anal dysplasia.<sup>8,9</sup> The presence of high risk HPV infection and presence of multiple HPV types is also increasingly found as the immune system fails in HIV positive MSM who have CD4 counts less than 200 cells/mm<sup>3</sup>.

### ANAL DYSPLASIA IN MSM

The diagnosis of anal dysplasia by means of anal cytology is similar to cervical cytology: variably sensitive and problematic. In a HIV positive MSM population, the sensitivity of anal cytology to screen for any anal cell abnormality approximates to that of the cervix when samples with atypical squamous cells of undetermined significance (ASCUS) are included in the “abnormal” category.<sup>10</sup> However, anal cytology specimens have limited specificity to reflect the anal lesions defined by biopsy at high resolution anoscopy (HRA); most cytology specimens are reported with abnormalities at the lower, more benign, end of the cytological spectrum, such as ASCUS or low-grade squamous intraepithelial lesions.<sup>11,12</sup> Additional challenges specifically related to anal cytological sampling include a limited number of clinicians willing and able to take the sample (although it should be noted that study participants with previous experience of anal cytology can self-take samples with adequacy rates of over 90%),<sup>13</sup> and availability of cytopathologists with expertise in reporting on these samples. Furthermore, without the local availability of clinicians trained in HRA, the presence of abnormal anal cytology can only serve to increase awareness of the presence of potentially pre-cancerous cells without defining the cellular abnormality.

The resulting clinical algorithm that has emerged from these observations is that any patient diagnosed with abnormal anal cytology should be referred for HRA as there is a high positive predictive value to detect any grade of anal dysplasia,<sup>11</sup> with biopsy of lesions suspicious for high-grade anal dysplasia based on validated cervical colposcopic criteria.<sup>14</sup>

Unlike the cervix where there is general agreement that high-grade cervical dysplasia progresses to cervical cancer,<sup>15</sup> the evidence for progression of anal high-grade dysplasia to cancer, although compelling, is mostly circumstantial. Anal dysplasia and anal cancer are both

associated with the same HPV risk types, the anal canal has a similar pathological response to infection with HPV as the cervix, anal and cervical epithelium has cellular changes reported using the same cytological and histological grading systems and display similar chromosomal abnormalities with increasing severity of dysplasia.<sup>16,17</sup> Additionally, high-grade anal and cervical dysplasia is frequently found overlying cervical and anal cancer, and there is a high prevalence of high-grade anal dysplasia in populations known to be at risk of anal cancer as well as the previously established progression of perianal high-grade dysplasia (Bowen's disease) to cancer.<sup>18</sup> One recent small observational study in the UK showed evidence of progression in a group of non-HIV infected immunosuppressed patients diagnosed with high-grade anal dysplasia who chose to undergo regular observation rather than treatment, with 50% progressing to cancer within a median of 5 years from the initial high-grade diagnosis. No-one treated for high-grade anal dysplasia in this study developed cancer.<sup>19</sup>

To date, the management of high-grade anal dysplasia has followed the surgical treatment paradigms developed for cervical dysplasia, although with limited success and high procedure-associated morbidity in a HIV positive population.<sup>20</sup> More recently, the emergence of infrared coagulation (IRC) has shown promise as a more efficacious, better tolerated and repeatable method of ablating high-grade dysplastic lesions in this population. From the two published studies of IRC treatment, successful ablation has been reported in 65–70% of cases at between 3 and 6 months following the procedure.<sup>21,22</sup> It of course remains to be seen whether treatment results in a decrease in the incidence of anal cancer in this population.

### ANAL CANCER

Unfortunately the presentation of anal cancer is far from specific and includes symptoms such as bleeding, pain and the presence of a mass. MSM are likely to have some degree of anorectal symptoms simply related to receptive anal intercourse.<sup>23</sup> Other anorectal conditions that are common in the general population are even more common in MSM and particularly prevalent in HIV positive MSM.<sup>24,25</sup> These conditions include haemorrhoids, anal fissure, anal abscess and fistulae. MSM are additionally at increased risk of anorectal sexually transmitted infections.<sup>26</sup> The unfortunate consequence of this situation is that MSM may present to

their primary care physician with undiagnosed anorectal symptoms that are often longstanding in nature due to being tolerated or ignored. This becomes particularly important when anal cancer is the cause of the symptoms as treatment outcome is critically dependent on the size and stage of the primary lesion and any delay in diagnosis will negatively impact prognosis.

Although there is the prospect of a prophylactic vaccine for HPV being available for boys and young men, there is a strata of HPV exposed MSM that will remain at risk of anal dysplasia and cancer. Unfortunately it is more than likely that this group of men are not aware of their risk. A recent study in Australia demonstrated that in a population of predominantly HIV negative MSM who regularly use medical services, 55% had never heard of HPV and less than 30% were aware of anal cancer risk factors that included having sex with men.<sup>27</sup>

### THE FUTURE

The lack of definitive evidence of progression, poor specificity of anal cytology and lack of referral opportunities has likely prompted many physicians and healthcare agencies to defer the institution of any form of anal cancer screening for MSM. This inertia has resulted in an unscreened, uninformed, population that are, for the most part, unaware of their increased risk of developing anal cancer. Although a strong evidence base is critical to inform healthcare policy, there is a high likelihood that, due to the nature of this condition, definitive answers to the above questions will not be forthcoming in the near future. However, this should not be a reason to abandon any attempt to address this issue from the perspective of the individual, the healthcare provider, community or government.

MSM, and particularly HIV positive MSM, need to know that they are at risk of this potentially fatal condition. Agencies and media with a focus on MSM healthcare in addition to advocacy groups have an obligation to address, inform and maintain awareness of this issue—as they have with other healthcare issues that disproportionately affect MSM, such as STI, psychiatric illness and substance use. Once informed, MSM will then be able to proactively seek advice on available preventive measures.

HIV positive MSM, more than any other male group, are more likely to regularly access medical services. This provides an opportunity for the institution of a proactive healthcare policy such

as that implemented by the US Centers for Disease Control in its recommendations for extended site STI screening in MSM. In the case of anal dysplasia this may range from healthcare information about the condition to anal cytology screening and HRA where available. As anal cytology is an imperfect tool it should be a research imperative for both funding agencies and scientific investigators alike to address methods by which screening may be improved to increase specificity and better inform referral pathways for those at highest risk of progression. Meanwhile healthcare providers should use their privileged access to engage at-risk individuals in discussing anal symptoms and provide education on HPV-associated pathology as well as guidance on when symptoms clearly warrant clinical examination and further investigation.

Ultimately it is unacceptable that 25 years after a UK government public information campaign to promote HIV awareness warned "Don't Die Of Ignorance" to have MSM dying, literally, of just that.

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