Anal cancer prevention strategies including screening for HPV-related diseases in HIV-positive patients

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One third of HIV+ve MSM worldwide have anal HPV16 infection.

80-90% of anal cancer is caused by HPV16.

Anal cancer prevention strategies

• **Primary Prevention**
  • HPV vaccination of MSM aged 16-45 in GUM/HIV clinics
  • HPV vaccination of adolescent boys
  • Prolonged ARV suppression
  • Starting ARVs at higher CD4 counts
  • Smoking cessation
HPV vaccination of MSM in GUM/HIV clinics

• The Joint Committee on Vaccines and Immunisation has given an opinion that a targeted programme of quadrivalent HPV vaccination of all MSM up the age of 45 years attending GUM and HIV clinics would be cost effective, provided the combined cost of the vaccine and administrative fee was below a certain threshold price (which is below the list price of the vaccine)

• The JCVI noted that before any programme could be undertaken work is required by DH, PHE, local government and NHS England to identify the commissioning arrangements, which is currently being taken forward

• Work on the implementation plans continue, but ministerial approval for the programme is still pending
HPV vaccination of adolescent boys

• This was last considered by the main JCVI in June 2015. Two models are being used for consideration, by (i) PHE and (ii) LSHTM. Full results were not available at that time. This is a complex area as it is necessary to look at scenarios of different combinations of doses (1 or 2), vaccines (2-, 4-, or 9-valent) and groups (girls, boys, & MSM).

• Preliminary conclusions were (i) programmes to vaccinate either girls only or boys only have similar effects (ii) either strategy evens out in the long term after 100 years (iii) gender neutral vaccination can achieve faster declines in disease (iv) longer delays in the introduction of gender neutral vaccination makes the strategy becomes less cost effective

• The topic remains on the HPV sub-committee agenda, and a recommendation is expected to be made by late 2016 / early 2017
Is prolonged ARV therapy associated with decreased AIN2/3 & anal cancer?

- 320 MSM median CD4 638, all HRA with biopises, 51% HSIL, OR 0.32 (95% CI 0.16-0.63) for men with cART > 24 months
  - Libois A, Sex Transm Infect 2016; online

- Study of the male HIV+ve US VA cohort, n=45,231. There was a significantly decreased risk of anal cancer for those with undetectable viral load >60% of the time OR 0.51, receiving cART within 5yrs of diagnosis OR 0.63, nadir CD4 >350 OR 0.34, nadir CD4 350-200 OR 0.42
  - Chiao EY, J AIDS 2013;63:631
Anal cancer is associated with low nadir CD4, current CD4, & smoking

• A case control study of anal cancer within the Swiss HIV Cohort Study showed significant associations for current smoking OR 2.59, low nadir CD4 count <50 OR 3.96, each decrement of 100 CD4s at nadir OR 1.53, each decrement of 100 CD4s at diagnosis OR 1.24

• The strongest predictor of anal cancer risk was CD4 count 7 years prior to cancer diagnosis, OR 14.0 for <200 vs >500 CD4

• Bertisch B, Am J Epidemiol 2013;178:877
Criteria for assessing a screening programme
- UK National Screening Committee
- Anal cancer prevention

- The Condition
  - The condition shall be an important health problem √
  - All cost-effective primary prevention interventions should have been implemented as far as practicable X
  - The natural history of the condition, including development from latent to declared disease, should be adequately understood X
Progression to, and spontaneous regression of, AIN 2/3

- Retrospective review 2004-2011, Sydney, pts who had anal cytology or HR anoscopy
- 574 subjects, 99% male, 73% HIV+ve, HIV-ve - median age 26 yrs; HIV+ve - 45 yrs; median CD4 nadir 216, 84% VL undetectable, FU 1.1 yrs median, 47% had AIN 2/3
- Progression rate to HGAIN was 7.4/100 py, progression to AIN3 was more likely with ↑age, and HIV, and ↓nadir CD4;
- 24/101 pts with HGAIN and 35/55 with AIN3 had regression (9 with treatment), 47% of AIN3 spontaneously regressed
- 4 pts had anal Ca, 2 at baseline, 2 during FU
- SPANC study, fully enrolled, will provide hard data
- French Malignant Progression of AIN3 study again similar
Criteria for assessing a screening programme
- UK National Screening Committee
- Secondary prevention

• The Test
  • There should be a simple, safe, precise and validated screening test √ (although high resolution anoscopy is a relatively complex screening test)
  • The distribution of test values in the target population should be known and the test should be acceptable to the population √
Digital ano-rectal examination (DARE)

- Two year prospective study in Melbourne of annual DARE in 327 HIV+ MSM
- DARE is highly acceptable to patients
- 86 men (27%) had an abnormality, 17 (5%) referred to a specialist, 1 had Anal Cancer, 3 had AIN3
- Cost-effectiveness analyses show that screening HIV+ MSM >50 yrs old every 4 years is the most cost-effective strategy ($19,650 per QALY gained)
  - Ong JJ, J Med Screen 2015; Oct 13 Epub
  - Ong JJ, J Int AIDS Soc 2016;19:20514
ANALOGY study

• Studied 203 HIV positive, 81 HIV negative MSM, using anal cytology, anal HPV testing and HRA
• 40% abnormal cytology, 10% HSIL
• 85% HR-HPV positive, 72% of men had a positive HRA
• In HIV +ve MSM, 3 cancers, 11 AIN3, total 7% prevalence
• 29% of AIN3 cytology negative

➤ Conclusions

• HRA was highly acceptable and is the screening test of choice
• Prevalence of AIN3 supports screening, but burden of lower grade lesions and AIN3 treatment limitations require consideration
  • Schofield AM, AIDS 2016 Epub
Could serial HPV viral loads predict anal disease evolution?

- Study of 76 anal cancers from France
- Used type specific real time PCR
- 98.6% HR HPV +ve, 89% HPV16 +ve,
- HPV16 viral load high, from $2.1 \times 10^3$ to $1.5 \times 10^7$
- HPV integration measured by E2/E6 ratio
- Of HPV16 +ve cases, 22% purely episomal, 70% both episomal and integrated, 8% purely integrated.
  - Valmary-Degano S, *Hum Pathol* 2013;44;992
Could serial HPV16 viral loads predict anal disease evolution?

Verhelst S, Eur J Cancer Prev 2016; Feb 17 Epub
Criteria for assessing a screening programme
- UK National Screening Committee
- Secondary prevention

• **The Treatment**
  • There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment ✗
  • There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered ✗
Current AIN 2/3 treatment options and outcomes

- Main treatment options ablation (laser, electrocautery, or infrared coagulator), Imiquimod, or 5-FU
- RCT showed Complete Responses of electrocautery (39%), Imiquimod (24%) and 5-FU (17%), but recurrences in 66% at 1.5 yrs
  - Richel O, Lancet Oncol 2013;14:346
- Long term study of 456 HIV+ve MSM receiving ablation showed recurrence rates of 53%, 68%, 77%, at 1,2,3 yrs, with 5 cancers
  - Goldstone SE, Dis Colon Rectum 2014;57:316
Studies underway that will add to the evidence base

- US RCT of either (i) ablation or topical treatment or (ii) observation of AIN 2/3 in HIV +ve MSM, ANCHOR study NCT02135419
- US RCT of either (i) imiquimod, (ii) 5-FU, or (iii) observation for AIN 2/3 in HIV +ve MSM, NCT 02059499
- Canada RCT or (i) ablation, or (ii) observation of AIN 2/3, HPV-SAVE, NCT 02503111
- Germany RCT of (i) TCA, or (ii) electrocautery for AIN 2/3, NCT 02615860
Opportunities in the UK for funding to support research into screening

• The Screening, Prevention and Early Diagnosis (SPED) Advisory Group of the National Cancer Research Institute (NCRI) is holding a workshop 25 May 2016

• The aim of this workshop is to help investigators develop ideas for studies which can subsequently be submitted as an application to a funding committee. Investigators have been invited to present brief outline proposals in the areas of screening, prevention or early diagnosis to discuss at the workshop.
UK clinics currently offering systematic anal cancer screening services including HRA

<table>
<thead>
<tr>
<th>Clinic</th>
<th>Contact Person</th>
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<tbody>
<tr>
<td>Homerton University Hospital, London</td>
<td>Dr Mayura Nathan &amp; colleagues</td>
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<tr>
<td>Chelsea &amp; Westminster Hospital, London</td>
<td>Dr Paul Holmes</td>
</tr>
<tr>
<td>56 Dean Street, London</td>
<td>Dr Gary Whitlock</td>
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<tr>
<td>10 Hammersmith Broadway, London</td>
<td>Dr Chris Scott</td>
</tr>
<tr>
<td>St Mary’s Hospital, London</td>
<td>Joint Wharfedale / Miss Deirdre Lyons clinic</td>
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<td>Royal Free, London</td>
<td>Dr Deepa Grover</td>
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How to prevent anal cancer in HIV+ve MSM – I have a dream ... 

GOOD

• Start ARVs at diagnosis in all HIV patients
• Discourage smoking
• Introduce a ‘Double DARE’ screening programme –
  • All get (i) HPV16 DNA test (ii) digital ano-rectal exam
  • If DARE +ve - refer to specialist HRA clinic
  • If HPV16 +ve – (i) Reflex HPV16 VL (ii) Follow up 1yr & 2yrs with repeat HPV16 VL. At 2yrs lab reports HPV16 VL evolution and guidelines indicate next stage in management
• Develop a new effective AIN3 treatment strategy based on ablation combined with a therapeutic HPV vaccine
How to prevent anal cancer in HIV+ve MSM

✈ BETTER

• **ADD** - Implement HPV vaccination of MSM up to 45 yrs in GUM & HIV clinics
• Start ARVs at diagnosis in all HIV patients
• Discourage smoking
• Introduce a ‘Double DARE’ screening programme –
  • All get (i) HPV16 DNA test (ii) digital ano-rectal exam
  • If DARE +ve - refer to specialist HRA clinic
  • If HPV16 +ve – (i) Reflex HPV16 VL (ii) Follow up 1yr & 2yrs with repeat HPV16 VL. At 2yrs lab reports HPV16 VL evolution and guidelines indicate next stage in management
• Develop a new effective AIN3 treatment strategy based on ablation combined with a therapeutic HPV vaccine
How to prevent anal cancer in HIV+ve MSM

❖ BEST

• **ADD** Implement gender neutral vaccination
• Implement catch up HPV vaccination of MSM up to 45 yrs in GUM & HIV clinics
• Start ARVs at diagnosis in all HIV patients
• Discourage smoking
• Introduce a ‘Double DARE’ screening programme –
  • All get (i) HPV16 DNA test (ii) digital ano-rectal exam
  • If DARE +ve - refer to specialist HRA clinic
  • If HPV16 +ve – (i) Reflex HPV16 VL (ii) Follow up 1yr & 2yrs with repeat HPV16 VL. At 2yrs lab reports HPV16 VL evolution and guidelines indicate next stage in management
• Develop a new effective AIN3 treatment strategy based on ablation combined with a therapeutic HPV vaccine
Many thanks to

- Ellie King, UCL
- Richard Gilson, UCL
- Mayura Nathan, Homerton Hospital

- And apologies to
Finally some advice from Sir William Osler

"One finger in the throat and one in the rectum makes a good diagnostician."