STD TREATMENT GUIDELINES TABLES: ANAL CANCER

Burden

Author/Citation	Study Design	Population, Sample Size	Outcome measures	Summary Points
Machalek D Lancet Oncol 2012	Systematic review	MSM, HIV infected and uninfected Studies of prevalence and incident of anal HPV, AIN and anal cancer stratified by HIV status Until Nov 1 2011	Prevalence estimates: • HPV (any or HR) • cytology abnormalities • histologic abnormalities Incidence: • HGAIN • anal cancer Note: in metaregression analysis heterogeneity noted in estimates of HGAIN prevalence between early studies (Ruiter 1994, Palefsky 1997) than in more recent studies (post 2008)	<u>Any anal HPV Prevalence</u> HIV-pos (92.6%, 95%CI 90.8-94.5) HIV-neg (63.9%, 95%CI 55.2-72.6) <u>HR anal HPV Prevalence</u> HIV-pos (73.5%, 95%CI 63.9-83.0) HIV-neg (37.2%, 95%CI 27.4-47.0) <u>HPV-16 Prevalence</u> HIV-pos (35.4%) HIV-neg (12.5%) Cytology (any abnormal) HIV-pos (57.2% 95%CI, 51.2-63.2) HIV-neg (18.5%, 95%CI 8.0-28.9) HGAIN * HIV-pos (29.1% 95%CI, 22.8-35.4) HIV-neg (21.5% 95%CI 13.7-29.3) *w/o Ruiter 1994/Palefsky 1997 HGAIN Incidence: HIV+ dePokmandy2011 (8.5%/yr 95%CI, 6.9-10.4) Palefsky (1998)(15.4%, 11.8-19.8) Cancer Incidence (per 100,000 py) HIV-pos all studies (45.9, 95%CI 31.2-60.3) HIV positive, Post HAART (1996) (77.8, 95%CI 59.4-96.2) HIV negative (5.1, 0-11.5)

Psychosocial aspects of anal cancer screening

Author/Citation	Study Design	Population, Sample Size	Outcome measures	Summary Points
Truesdale Int J STD AIDS 2010	Retrospective and, cross sectional for risk factors	N=195, HIV-pos MSM and HIV neg MSM <u>Acronyms used in study</u> RF-Regular Follow-up, screening within 1 year LTF-Lost to follow-up for more than 1 year (telephone survey) LCB-LTF for >1 yr but then Came Back >=1 time within 6/07-3/08	Identify factors associated with screening compliance N=96 RF, 49 LCB, 50 LTF Demographics, sexual activity, insurance, HIV status, symptoms, emotional upset re: diagnosis, program issues (difficulty scheduling appts, bothersome being screened, pts understand how to get results) All univariate (no modeling)	Being upset by dx made RF more likely than LTF OR 3.26 (1.72-6.18) Symptomatic more likely to be RF OR 4.38 (1.42-13.51) HSIL dx more likely RF than LTF OR 3.73 (1.8-7.71) Program issues NS 18% of LTF pts who participated in survey returned for screening All univariat ORs
Tinmouth et al 2011	Prospective cohort, follow up at 4 times points over 6 mo	N=104, HIV positive MSM	Change on QOL or other psych scales Impact of events, illness intrusiveness ratings, psychological consequences, Hospital anxiety/depression, HIV symptom index	No adverse impact on anxiety/depression Greater impact in those with higher baseline distress, HIV-related symptoms, younger age
Landstra et al Psycho-oncology 2012	Prospective cohort, f/up 3 times over 3 months	N=163, HIV positive men	Change on QOL or other psych scales Anal screening questionnaire, Cancer Worry scale, distress thermometer, MOS SF12, Depression anxiety stress scale	No adverse psych impact (anxiety/ depression, stress, QOL) Increases in cancer-specific worry, anal health and health optimism impacted, rebounded back for those reassured by histo results, worse for those with HGAIN

Performance of screening modalities-Cytology (studies where all pts received HRA regardless of cytology result)

Author/Citation	Study Design	Population, Sample Size, Methods	Outcome measures	Summary Points
Berry DCR 2009	Cross sectional	MSM N=125 HIV pos = 35 (28%) HIV neg= 85	Sensitivity, specificity, NPV, PPV of cytology (ASCUS+) and HPV testing for detection of AIN2+histology	Prevalence AIN2+=30% HIV+ ASCUS+ Sensitivity-87%, Specificity 41%, PPV 57%, NPV 82% HIV- ASCUS+ Sensitivity-55%, Specificity 76%, PPV 42% NPV 84%
Mathews PLoS one 2010	Retrospective	HIV pos men N=261 MSM	ROC (area under the curve) and Sensitivity, specificity, NPV, for AIN2+ histology Cytology HSIL or ASC-H 3 adjustments 1): sen/sp of HRA directed biopsy is 74%/91%-like for CIN/colpo 2)HRA biopsy gives no False pos 3) Latent class analysis-conditional probability model to estimate sen/sp	Prevalence AIN2+ 24% ROC for cytology 0.78 (0.72-0.85) Sensitivity-66%, (0.5-0.81) Specificity 90% (0.85-0.95) With adjustments, estimated range of sensitivity 47-89%, and
Mathews PLoS one 2011	Meta analysis	N=11 included studies for anal QUADAS tool for dx test accuracy studies	ROC comparing Anal cytology versus cervical cytology for detection of high grade lesions CIN2+ or AIN2+ 1) Area under curve 2) Gold standard HRA	ROC 0.70 (0.66-0.735) for anal ROC 0.83 (0.81-0.86) for cervical Anal cytology slightly less discriminating than cervical
Nathan AIDS 2010	Cross sectional	N=495 (93% men) For HGAIN analysis, N=276	Sensitivity, specificity, NPV, PPV of cytology (cut off not specified ?ASCUS+) to detect HGAIN	Sensitivity 81% (70-90) Specificity 37% (30-44) PPV 30% (24-38) NPV 85% (76-92) Estimates maybe biased b/c everyone received HRA but not all patients who received HRA were included in estimates Found that

Performance of screening modalities-part 2

Author/Citation	Study Design	Population, Sample Size, Methods	Outcome measures	Summary Points
Salit AIDS 2010	Cross sectional	HIV pos MSM, N=401 All received cytology, hpv testing and HRA results TRACE study	Sensitivity, specificity, NPV, PPV of cytology (ASCUS+) and HPV testing for detection of AIN2+	Prevalence abnl cytology: 67% Prevalence AIN2+=25% Cyto: Sensitivity-84%, Specificity 39% PPV 31%, NPV 88% Onco HPV: Sensitivity 100%, Specificity 16%, PPV 28%, NPV 100%,
HRA FOR SCREENING				
Gimenez 2011 Arq Gastroeneterol (Portuguese)	Cross sectional	HIV-pos, N=128 (gender not specified) All received HRA/biopsy, HPV testing, all normal HRA also had routine biopsy at 7 oclock	Sensitivity, specificity, NPV, PPV of HRA/Biopsy for detection of ASIL (both LSIL and HSIL)	Sens: 90% Spec: 19% PPV: 42% NPV: 75% Cannot determine test performance for detection of HGAIN

Performance of screening modalities-Biomarkers

Author/Citation	Study Design	Population, Sample Size, Methods	Outcome measures	Summary Points
Salit et al. Cancer Epi Biomarkers 2009	Cross sectional	HIV pos MSM N=224 from TRACE Study All had cytology, HPV testing, HRA HPV infection (16, 18, 31), HPV VL, # of genotypes, p16 RNA quantification, E6/E7 transpcripts	Sensitivity, specificity, NPV, PPV of biomarkers for detection of AIN2+	33% HGAIN prevalence HPV16: Sens 53%, Spec 69% PPV 45%, NPV 75% Higher HPV16 VL in pts with HGAIN vs LGAIN, (p=0.003) HPV 16 VL ≥100 copies: 95% sens, 28% spec HPV 16 VL ≥5000 copies: 38% sens, spec 85% None of the HPV types 16, 18, 31 had high sensitivity, No association with P16 or E6 transcripts and HGAIN
Scarpini Cancer Epi Biomarkers 2008	Prospective but data pooled and analyzed cross sectionally	Pts group referred for anal warts or suspected AIN N=119 patients (suspected ds) (mostly HIV pos, exact % not indicated, 108 male) and N=25 partners w/o suspicion of disease Pts& partners received cytology, HRA, w biopsy if abnormal. 4 partners also gave biopsies of normal appearing tissue 59 people gave multiple samples over time, results pooled, x sectional 108+22 patients produced 211 adequate samples (cyto+ HRA or histo)	Sensitivity, specificity of ≥3 cells expressing Minichromosomal Maintenance Proteins (MCM2 MCM5) as determined by IHC for detection of any lesion and for AIN2+ HRA/histology as gold standard	211 adequate samples: Any lesion: sens 79% (73-85) Specificity: 77% (0.64-0.90) AIN2+, Sens: 84% (0.75-0.93) (specificity not listed, not in supplement either) (no differences in performance between HIV+ and HIV-)
Wentzensen et al AIDS 2012	Cross sectional	HIV pos MSM N=363 receiving screening at Kaiser Northern CA	Sensitivity, specificity, NPV, PPV of biomarkers for detection of AIN2+	Among HPV-related biomarkers Youden's index was highest for HPVe6/e7 mRNA (YI=0.422)

		All received HRA, cytology, hrHPV testing, HPV 16/18 testing, e6/E7 mRNA (HPV 16, 18, 31, 33, 45) p16/ki-67 dual stain on cells from swabs	Composite AIN2+ =cytology or histology AIN2+ Youden's index=sensitivity + specificity -1 (gives equal weight to sensitivity and specificity)	Sens 79.8% (70.6-86.8) Spec 62.4% (55.5-68.9) PPV 50.9 % (43-58.8) NPV 86.4% (79.7-91.2) p16/ki-67 cytology with ≥5 cells positive had Youden's index of 0.58 Sens 77.6% (68.3-84.8) Spec 73.2% (66.8-78.8) PPV 58 % (49.5-66.1) NPV 87.2% (81.4-91.5)

Programmatic considerations

Author/Citation	Study Design	Population, Sample Size	Outcome measures	Summary Points
Siekas AIDS Reader 2009	Retrospective cohort Nov 07-may 08	HIV infected men, 95% MSM N=150 cytology N=122 underwent HRA/biopsy	% no-show for follow/up Complications (bleeding, pain, infection) Descriptive issues with billing and reimbursement	10% no show rate No complications reported No difficulty with reimbursement using CPT code 46600 and modifier 22 for HRA Or 46606 if biopsies done Reimbursement $60-Medicare $150 Private insurers

Prevention of recurrence

Author/Citation	Study Design	Population, Sample Size, Methods	Outcome measures	Summary Points
Swedish, Goldstone CID 2012	Prospective, non concurrent cohort f/up 1 mo after 3rd qHPV dose	HIV negative MSM, N=202, single center practice (SG) previously treated HGAIN, N=88 vaccinated w qHPV x3, (6/07-12/10) N=114 not vaccinated (4/07-12/09) f/up frequency not defined, date of study entry not defined for unvaccinated HPV testing done for those w insurance coverage	Recurrent HGAIN on biopsy	Baseline vax pts younger, unk race, h/o EGW Post qHPV: 12/88 had recurrence, incidence 10.2/100 py (5.3-17.8) no vax: 35/114 had recurrence, 15.7/100py (10.9-21.9) Yr1: HR 0.42 (.22-.82) p=0.01 Yr2: HR 0.50 (0.26-98) p=0.05 (n=129) Yr3: HR 0.52 (0.27-1.02) p=0.06 (N=73) (similar findings for those with hrHPV positive, n=105)

HGAIN Treatment

Author/Citation	Study Design	Population, Sample Size, Methods	Outcome measures	Summary Points
Macaya Cochrane Library 2012	Systematic Review	Searching for randomized controlled trials that assessed any intervention for anal canal intraepithelial neoplasia	Primary Endpoints • AIN eradication (presence of normal epi or scarring, absence of AIN) • HPV eradication (at 4 12 or 48 weeks after treatment) • Anal cancer Secondary endpoints • Downgrading from HGAIN to LGAIN • Recurrent disease • QoL, adverse events	N=1 RCT (Fox 2010) 22 excluded for being uncontrolled or retrospective or missing key data Cranston 2008, Goldstone 2011, IRC Marks 2011 (IRC or electrocautery) Jay 2009, Richel 2010 5FU Singh 2009 TCA Stier 2008 IRC (in prior evidence table)
Cranston Int J STD AIDS 2008	Retrospective	N=68 HIV positive MSM with 78 HGAIN lesions (no more than 50% circumference)treated with IRC, re-biopsy of treatment site after treatment (mean=140 days)	Efficacy of treatment (either normal or downgraded histology)	74 lesions were biopsied after tx 8 Normal, 39 were AIN1 (64% efficacy) 27 remained AIN2/3
Fox AIDS 2010	RCT	HIV positive MSM with HGAIN N=64 randomized, double blind Imiquimod vs placebo 3x week x 4 months (1/2 sachet) Cytology, HRA, biopsy 2 mos post imiquimod Open label imiquimod for 4 more mos if no resolution. Q 6 mos surveillance Mean duration of f/up 36 mos	Primary endpoints Improvement of HGAIN: Clearance of AIN, downgrading of HGAIN to LGAIN at 6 mos, sustained at 1 year	11 did not complete study (1 withdrew due to side effects) 53 completed study=28 imiquimod/25 placebo 4/28 pts resolved in imiquimod arm compared to 1/25 placebo (NS) 8/28 downgraded to LSIL-imiquimod arm 1/25 in placebo Anal CA (few weeks after initiating protocol) For composite outcome of downgrade or resolution, imiquimod was associated with a positive outcome (P=0.003)

		Originally powered at N= 120 pts, sample size achieved (n=53) α=0.05 and β 0.90 assuming 40% regression for tx group and 0% for controls.		
Goldstone Dis Colon Rectum 2011	Retrospective	N=96 MSM (40% HIV+) Underwent IRC for HGAIN and had at least 1 yr follow-up Median f/up HIV+=69 months HIV-neg=48 mos	Recurrence of HGAIN or progression to CA after treatment	Loss to f/up >30% for both HIV+/HIV- HIV+ (N=44), HIV- (N=52) recurrence rates of HGAIN at 1 year post 1st ablation: 38% of HIV- MSM, 61% of HIV+ MSM Over course of study, 62% HIV-MSM and 91% of HIV+ MSM recurred at some point No cancers, no serious adverse events
Marks J Acquir Immune Defic Syndr 2012	Retrospective	N=232 MSM, 57% HIV-positive Treated with electrocautery ablation (ECA) for anal canal HGAIN Median f/up 19.0 mo HIV+, 17.5 mos HIV-negative 3m post op=standard anoscopy 6m post op=HRA + cytology 12m=cytology +standard anoscopy (only those w HSIL or gross lesion went on to HRA)	Recurrence after treatment and progression to anal CA	Probability of cure for individual lesion was 85% for HIV neg , 75% for HIV+ MSM Recurrence rate after first ablation was 53% HIV-negative,63% HIV+ MSM (majority metachronous) 1 patient developed anal SCCA despite multiple rounds of ECA No serious adverse events noted (post-procedure diaries not utilized) IP: Overestimates success of ECA b/c required HSIL cytology or gross lesion at 12 months before HRA for tx failure
Nathan Int J STD AIDS 2008	Retrospective	N=181 patients referred for "anal canal disease" from other providers N=88 (48.6%) with HGAIN Treated with Imiquimod, excision, laser or various combinations of the 3 F/up at 6 mos post tx and then	Disease free status at 12 months Median time to cure for entire cohort	63% were disease free at 12 months after treatment, no cancers observed No comment on recurrences Median time to cure for whole cohort was 31 months (95% CI 23-40)

		annually thereafter if neg HRA Median f/up 19 mos		
Pineda Dis Colon Rectum 2008	Retrospective	N=246, 84% men, 74% HIV+ All treated with electrocautery in OR, minimum f/up of 2 months All with circumferential or near circumferential disease Avg f/up 41 months	HSIL recurrence-free survival	N=34 had staged procedures (two of these developed CA after OR, 2 died of AIDS) N=200 did not have staged procedures, 14 had CA on first trip to OR N=114 (57%) of 200 recurred, mean time to recurrence 19 mos. No difference according to immune status or CD4 count. 77% of these were tx as outpt, 23% repeat OR <4% complications (serious bleeding, anal stenosis, anal fissures, MI, cellulitis)
Richel 2010 British J Dermatology	Prospective open label trial	N=46 HIV+ men (x% MSM) w AIN 74% (n=34) with HGAIN 5FU twice weekly for 16 weeks Visits q 4-8 weeks, f/up visit for efficacy at 4 weeks post tx and at 6 mos for responders Breaks allowed up to 1 week for pts w side effects	Complete response: Clinical and histological resolution of AIN Partial response: regression from HGAIN to LGAIN HPV types and hrHPV viral loads	26/46 (57%) had complete or partial response 2 d/c due to side effects 6 mo f/up: 6/24 HGAIN (25%), 7 LGAIN 11/24 no disease No pts progressed to cancer HPV16 VL decreased w 5FU tx IP: Used anal applicator, gyn protocol of 2x week, probably missed anus and put most of cream into rectum.
Singh J AIDS 2009	Retrospective	N=54 MSM, 64% HIV+, 28 patients with HG, 55 lesions (biopsy or cytology if no biopsy done or contraindicated) TCA, then repeat exam 1-2 mos Up to 4 treatments allowed, then f/up 3mos, 6 mos 12 mos If not totally clear after 4 TCA, or recurred after initial clearance, then IRC or Surgery	Clearance: no AIN post Tx Regression: No AIN or LGAIN after tx Recurrence: any AIN after complete resolution	Of 55 lesions, 64% resolved, 7% downgraded Of 28 patients w HGAIN, 61% had regression to LGAIN or normal, 32% were completely normal In 21 patients who cleared, AIN recurred among 75% within mean period of 6 mos No serious side effects
Sirera AIDS 2013	Retrospective	N=69 HIV-infected patients (80% men)	Normal anal cytology after treatment	56/66 had an adequate f/up period of 12 months. All had normal cytology

		68 had only 1 lesion, 1 had 2 lesions Mean f/up was 25 mos		No HRA done if cytology normal After further follow up, 7 pts (12.5%) had abnormal cytology, Mean time to abnl cytology was 30 mos (Bx results: AIN1 4 pts, AIN2 3 pts, no cancer) IP: Overestimates success b/c no HRA done if cytology normal. Patients with limited disease
Weis Dis Colon Rectum 2012	Prospective	N=124 HIV-positive men and women with HGAIN 42-delayed tx or chose no tx (mean f/up 1.79 years) 82-immediate treatment with IRC mean f/up 1.28 years Those who delayed tx are counted twice, once in each group	Presence of HGAIN on biopsy	For immediate tx grp time to tx completion =1.1 yrs For delayed tx group=2.3 years CD4 nadir lower in delayed tx group 2 anal cancers in delayed tx group Of 98 with HGAIN who were treated, final histology was 3% normal, 70% LGAIN, 25% HGAIN Of 42 pts not treated, 7.1% were LGAIN, 88% remained HGAIN, 2 cancers

AIN Natural History

Author/Citation	Study Design	Population, Sample Size, Methods	Outcome measures	Summary Points
DePokomandy CID 2011	Prospective cohort	N=247 HIV+ MSM on HAART f/up q6 mos (median f/up 38mos) HPV testing, HRA for all at baseline and at least annually	Incident HGAIN /1000 pm Cumulative incidence HGAIN (Regression not measured)	N=147 no baseline HGAIN and adequate HRA f/up results 12.8 cases/1000 pmos (9.8-16.5) CI 24 mos: 23.1%, CI 36 mos: 36.6% For N=119 with 1st 2 HRA results negative: 7.1 cases/1000 pmos (4.9-10.2) CI 36 mos: 21.3% (8.5%/yr-see Machalek JID 2011) CI after 24 months by HPV type at baseline HPV16=64% (53-74) hrHPV (not 16)=40% (31-49) LR HPV or no HPV=7% (2-26)