Northwest AIDS Education and Training Center

Anal Cancer: Should Screening be Routine?

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Presentation prepared by:
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Criteria for a New Screening Intervention

1) Does the burden of disease warrant action? Is this an important medical problem?
2) Are the components of the intervention known to be effective?
   a) Anal paps & high-resolution anoscopy and biospy
   b) Treatment of abnormal lesions
3) Can providers manage this and will patients comply with a screening program?
4) Does early diagnosis and treatment change clinical outcomes?
5) Can we afford this?

Adapted from Chaio EY. CID 2006:43:223

HPV Epidemiology

- Anal cancer is caused by human papillomavirus (HPV)
  - Over 80 types – most do not cause cancer, types 16 and 18 most common causes of cervical and anal cancer
- Most people have been infected with at least one HPV type
- HPV prevalence in HIV+ MSM ~90% - 72% have ≥1 oncogenic type

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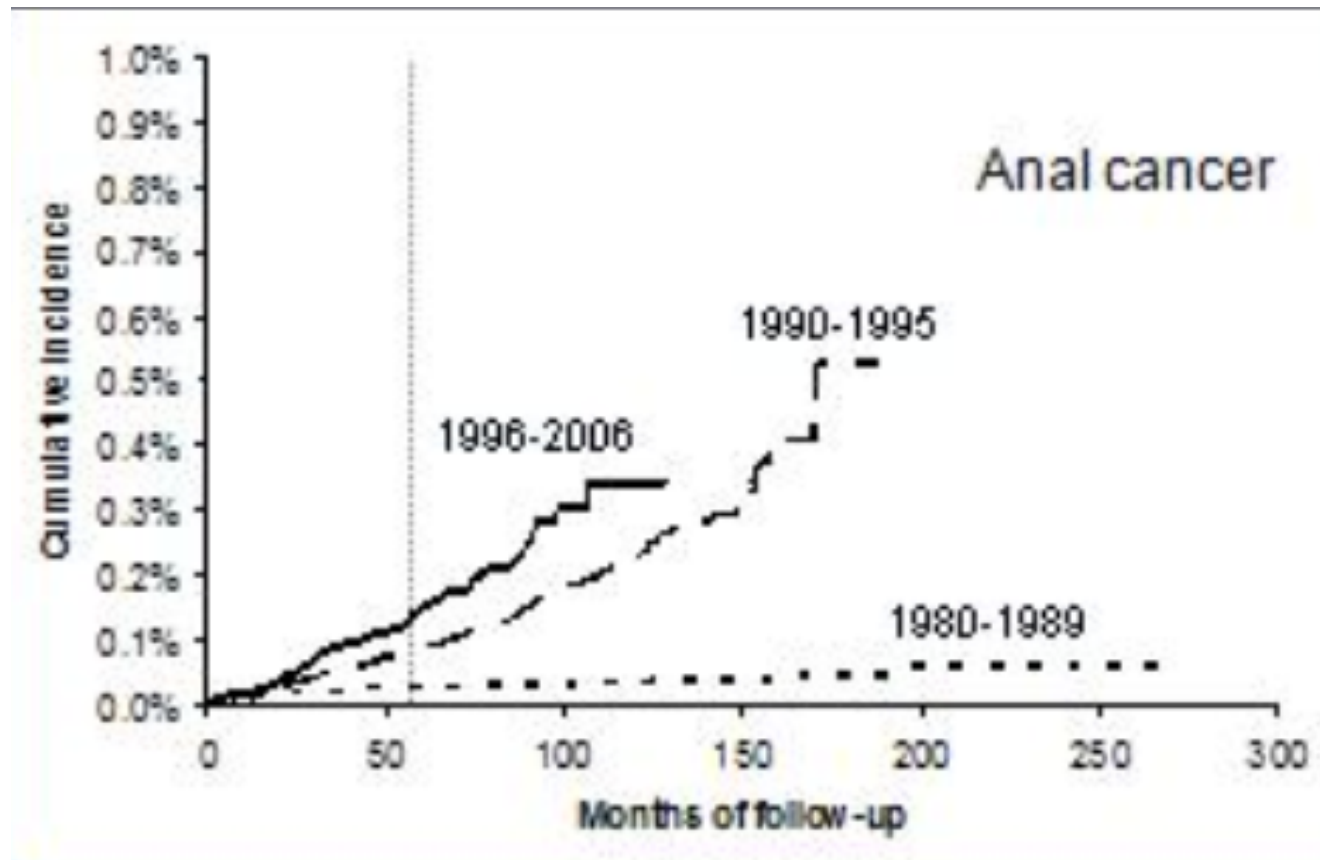
Anal Cancer: A Rare Cause of Death, But Rates are Rising

- Rate anal cancer among HIV+ MSM ~46/100,000 (range 13-131)
- 2003-06 San Francisco – 8 (0.6%) of 1161 deaths in persons with AIDS



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Anal Cancer and CD4 Count

NA-ACCORD Rate Ratios
Anal Cancer

CD4 Count	RR
<200	1.0
201-349	0.5 (.3-.7)
350-499	0.5 (.3-.7)
≥500	p.2 (.1-.3)

Anal CA also associated MSM, older age, calendar yr (1996-99)

- Antiretrovirals don't lower the risk
- Trend toward more anal cancer
- Divergent trends
  - People aren't dying of other things – more time to get anal cancer
  - If fewer people have low CD4 counts, that should decrease anal cancer risk

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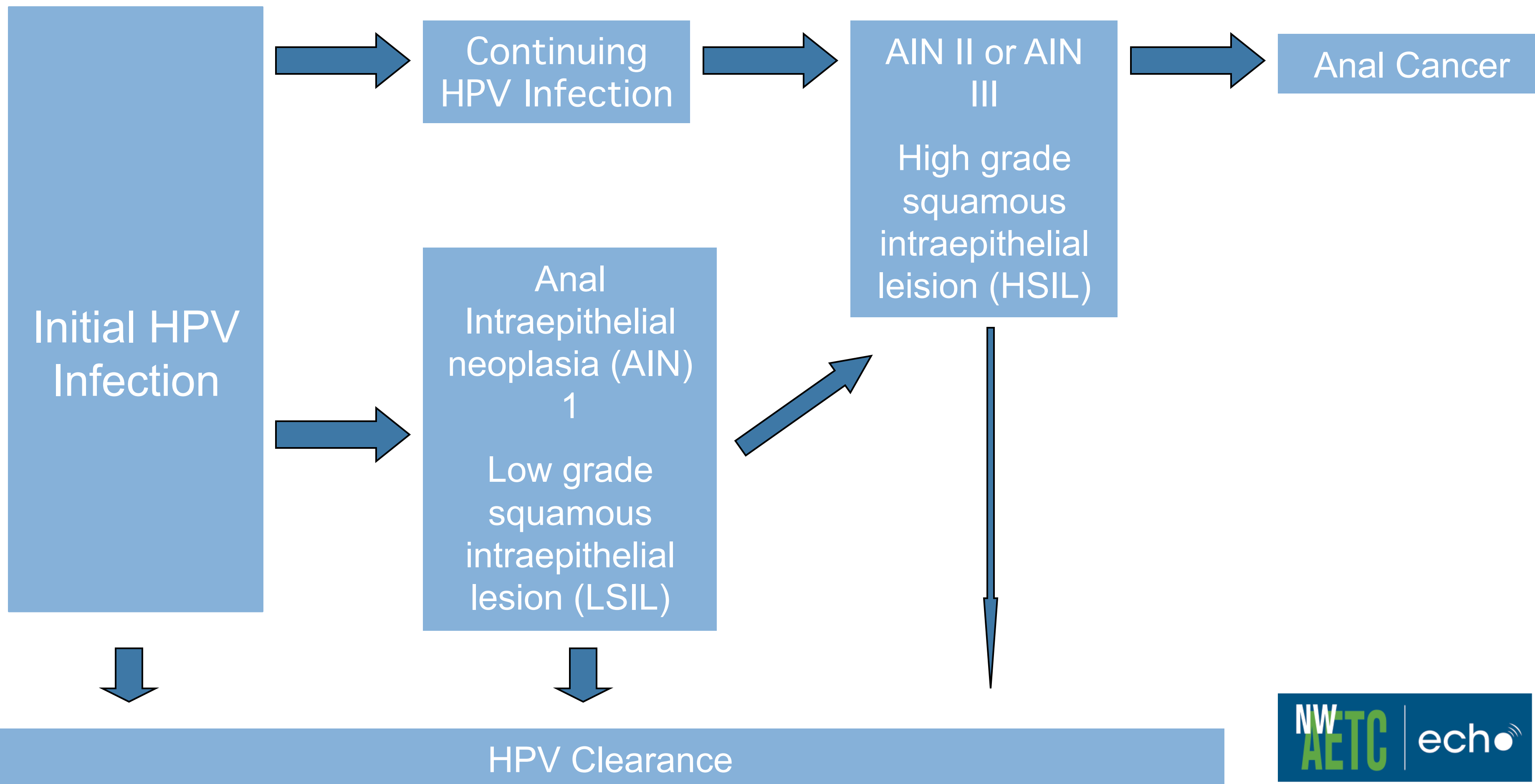
Anal Cancer Natural History

- Like cervical cancer, anal cancer is thought to progress from a precancerous lesions, anal intraepithelial neoplasia (AIN)



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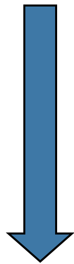
Anal Cancer Screening Algorithm

Anal Pap



Prevalence abnormal pap

HIV+ = 41-97%

HIV- = 4%

HIV+

Sensitivity=70-90%

Specificity=30-60%

HIV-

Sensitivity=25-50%

Specificity=92-98%

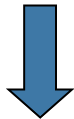
PPV

HIV+ = 38-46%

HIV- = 35-56%

High resolution anoscopy & biopsy

Among HIV+ men receiving serial PAPs, most will need high resolution anoscopy and biopsy.



Treatment

Only HSIL are treated. Approximately 5-9% of those with an abnormal anal Pap have HSIL

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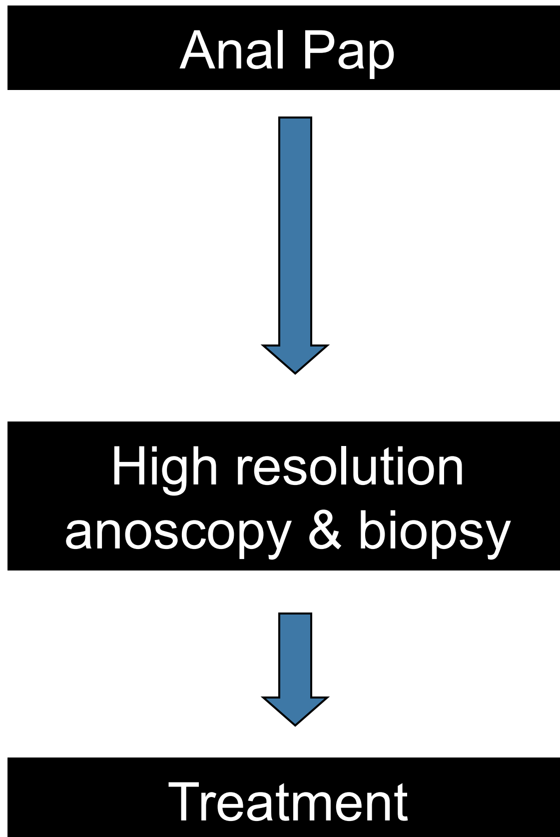
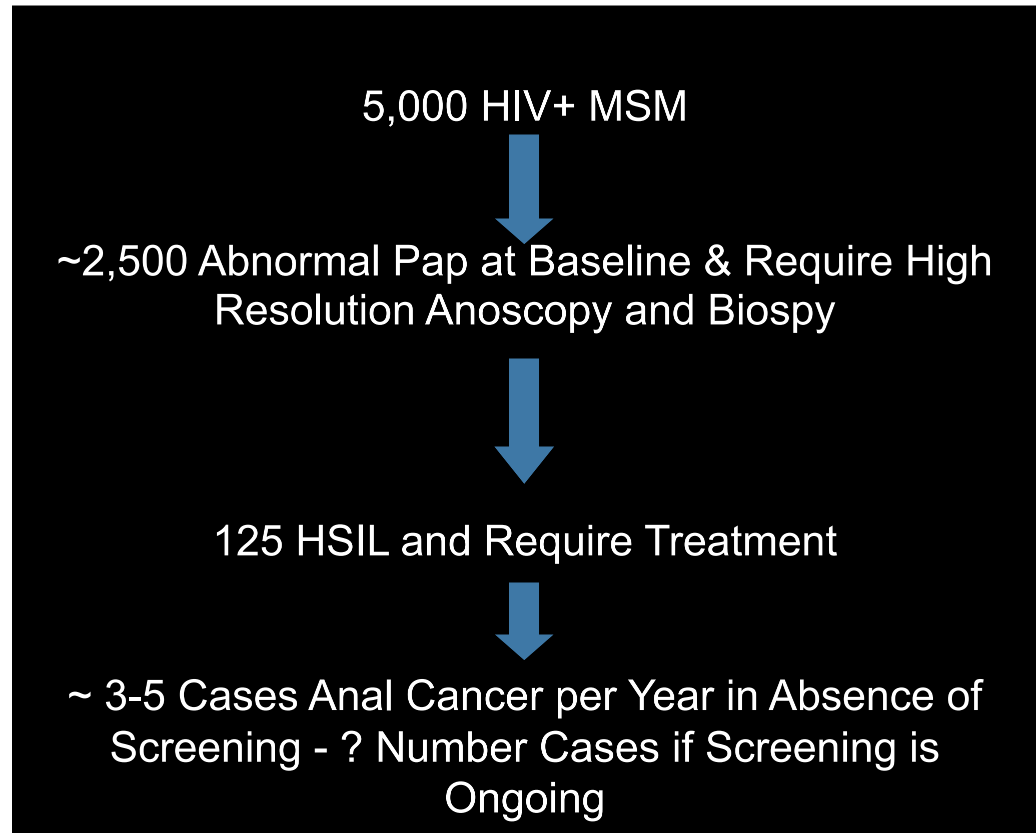
Anal Cancer Screening Algorithm





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Randomized Trial for AIN: Imiquimod, Topical 5-FU, Electrocautery

- 148 HIV+ MSM (60% HGAIN)
- 16 wks Rx – Imiquimond 3x/wk, 5-FU 2x/wk, electrocautery monthly
- Follow-up at 6 months

	4 Week Response ITT (95% CI)		Recurrence 6 Months	Severe Pain
	Complete	**Partial**		
Imiquimond	**26% (13-39)**	**13% (6-25)**	**21%**	**43%**
5-FU	**17% (8-30)**	**13% (5-25)**	**38%**	**27%**
Electrocautery	**41% (28-56)**	**7 (2-18)**	**17%**	**13%**

P=.04

Richel, O. CROI 2012

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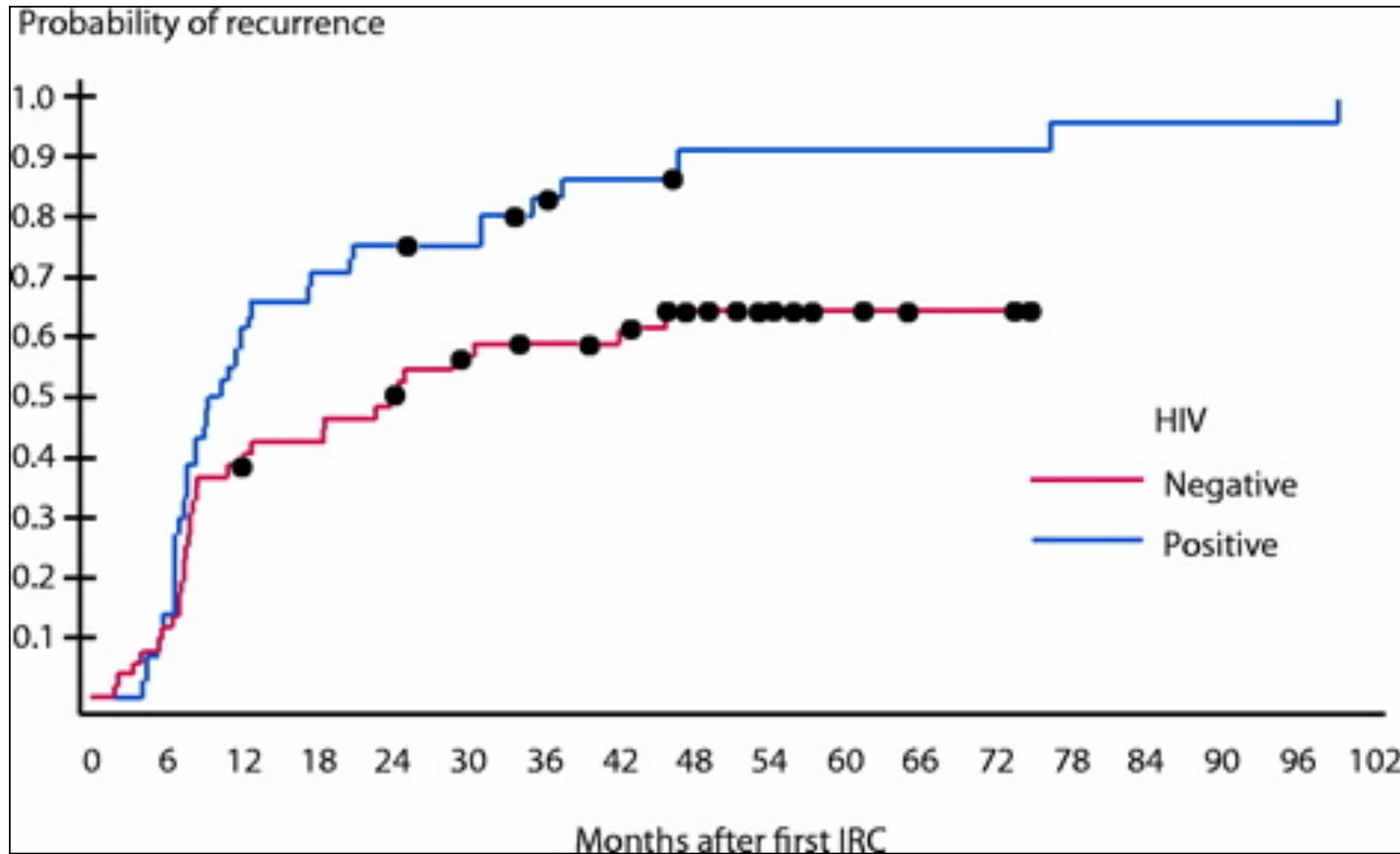
Recurrent of High-Grade Intraepithelial Squamous Lesions Among 96 MSM Following Infrared Coagulator Ablation



Goldstone R. Diseases of the Colon & Rectum; 2011. 54:1284-92.

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Patient Adherence

- In a prospective study, ~80% of 608 participants completed at least one follow-up visit. (Palefsky J. JAIDS 1997)
- 642/1864 (34%) of MSM screened in San Diego completed at least one follow-up screening visit within 3 years (Matthews J. JAIDS 2004)

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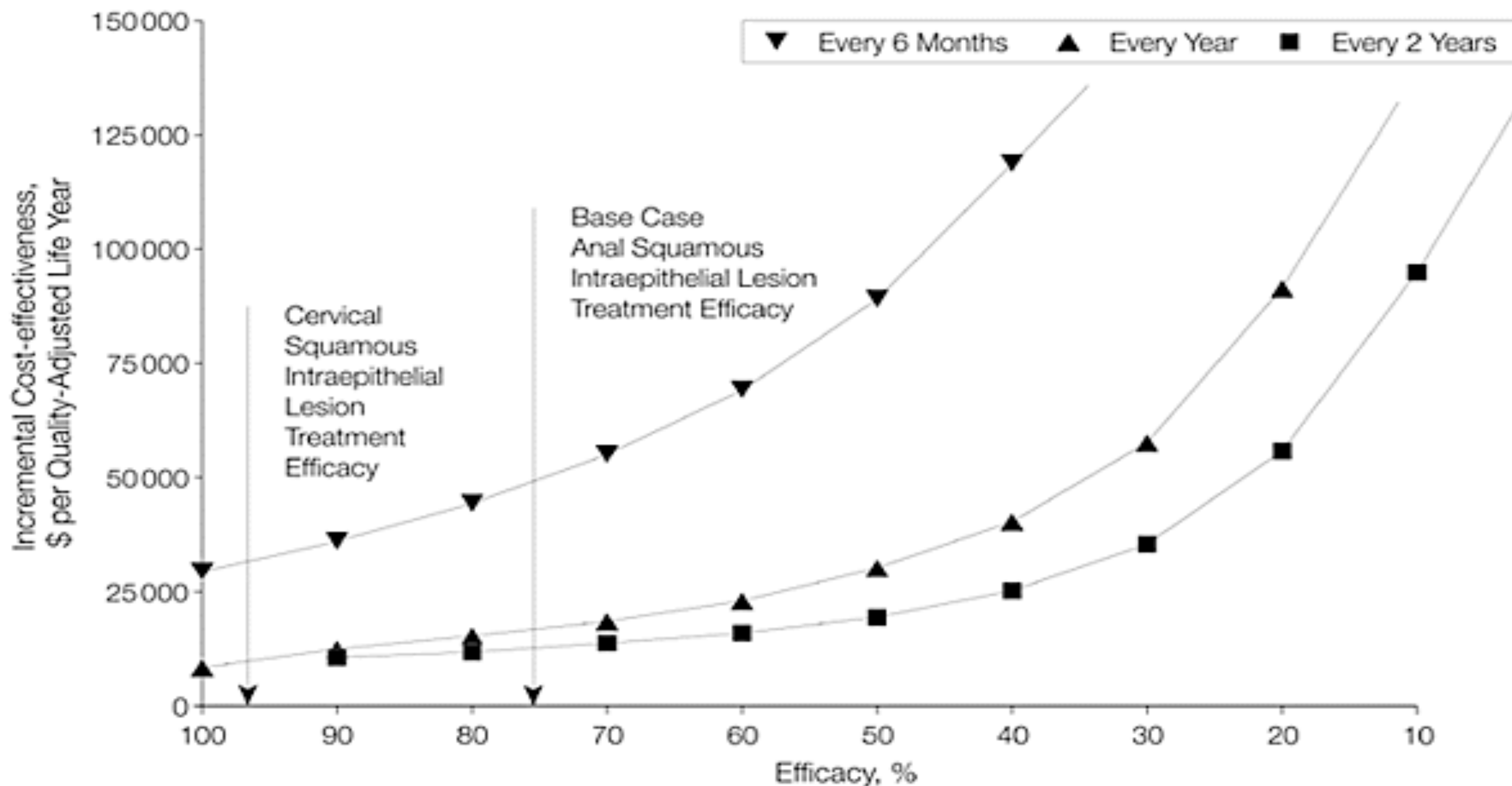
Efficacy of Treatment of High-Grade Anal Squamous Intraepithelial Lesions



Goldie, S. J. et al. JAMA 1999;281:1822-1829.

JAMA

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Argument for Anal Cancer Screening

- Anal cancer is an important and increasing cause of morbidity and mortality in MSM, particularly HIV+ MSM
- Anal Paps can identify abnormalities that are probably precursors to anal cancer
- Some evidence suggests that treating these abnormalities decreases their progression to anal cancer
- Some evidence to suggest that screening can be cost-effective
- Although there is no direct evidence that screening decreases anal cancer morbidity & mortality, Pap smears are thought to prevent cervical cancer, the rationale for screening for anal cancer is similar, and definitive trial are not likely to occur

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Argument Against Anal Cancer Screening

- Anal cancer is an important problem
- Anal pap results are very nonspecific, particularly in HIV+ men, meaning that most people will need biopsies
- Treatment is not known to be effective, existing evidence is very limited and rates of recurrence appear to be high
- Analogy to treatment for cervical cancer may be false
  - Loop excision for cervical cancer removes a much larger area of affected tissue
- It is uncertain whether providers and patients will comply with recommendations
- Experience with other cancer (e.g. prostate) screening should be a cautionary tale

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Criteria for a New Screening Intervention

Criterion	Answer
1) Does the burden of disease warrant action? Is this an important problem	Yes
2) Are the components of the intervention known to be effective? a)Anal paps & high-resolution anoscopy and biospy b)Treatment of abnormal lesions	Uncertain
3) Can providers manage this and will patients comply with recommendations?	Uncertain
4) Does early diagnosis and treatment change clinical outcomes?	Uncertain
5) Can we afford this?	Uncertain

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Recommendations

- New York State Department of Health recommends anal paps for persons with HIV
- CDC, the U.S. Preventive Services Task Force, the American Cancer Society, and the Infectious Diseases Society of America, **do not** recommend routine anal cytology screening
- If anal pap is done:
  - Baseline anal pap
  - HIV+ - twice in first year, then annually
  - HIV- men – baseline and then every 2-3 years
  - Referral for high-resolution anoscopy if cytology shows atypical squamous cells of uncertain significance or worse

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Can We Know if Screening Works?

- I' m not sure
- It's not clear that we can do a large enough study to answer the question
- What outcome would be enough to convince one that the screening was helping the population?
- Cancer death, the outcome used in the prostate cancer studies, would probably require tens of thousands of people followed over many years
- If anal cancer (not death) is the outcome, one would probably need many thousands of people followed over many years to answer the question. Screening might increase detection.
- Fewer people would be needed for an AIN outcome, but would that be convincing?

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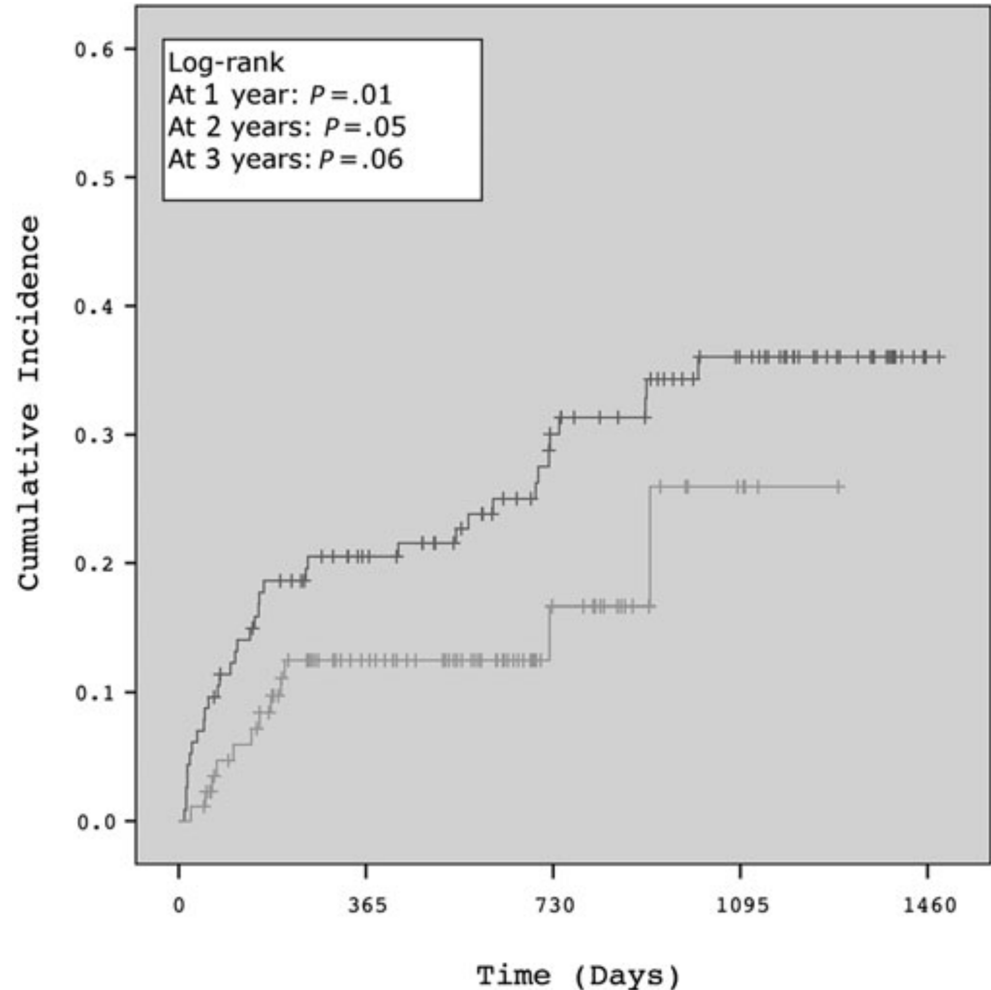
HPV Vaccine and Anal Cancer

- In a RCT, quadrivalent HPV vaccine 76% effective in preventing HPV 16,18, 6 and 11 associated AIN among MSM without prior HPV infection (NEJM 2011, 365:1576)

- Observational data in MSM Among MSM treated for high-grade AIN (HGAIN), recurrent HGAIN was less common men who also received qHPV vaccine (CID 2012)



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My Conclusions

- Anal cancer is an important and probably growing problem among HIV+ persons - Relatively rare cause of death
- The rationale for anal pap testing is strong, and screening is probably safe when provided by experienced persons
- The effectiveness and cost-effectiveness of screening is unknown, and it is not certain it is knowable
- Optimally, MSM should know about anal PAPs & have them available
- Existing data are not strong enough to make a firm recommendation that MSM should be screened
- Treating PLWHA while their immune systems are strong, which is justified for other reasons, should help prevent anal cancer.
- All young men (age $\leq$26) should be vaccinated for HPV. Role in older MSM uncertain.

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