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Disclosures

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Cervical cancer control in developing countries: Impact of HIV infection

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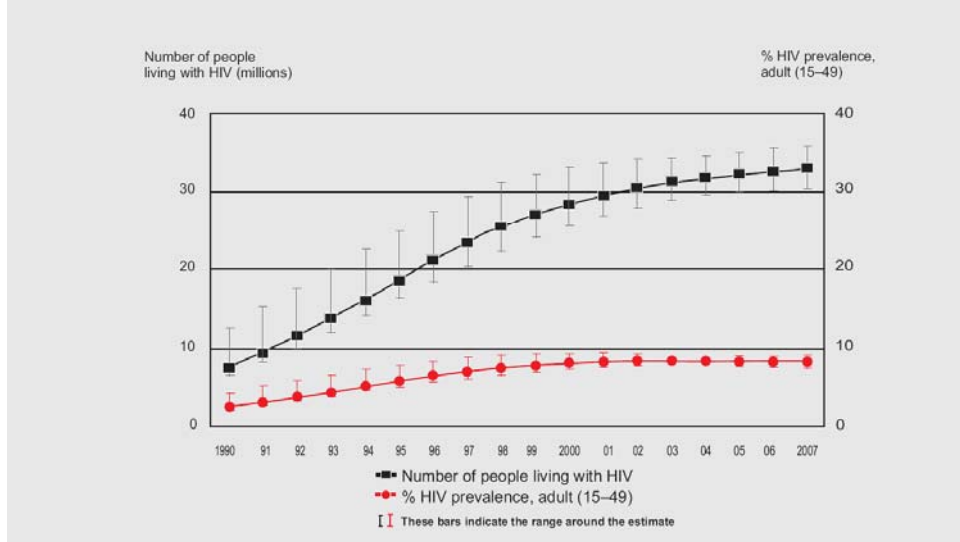
Estimated HIV prevalence in Sub Saharan Africa

- 1.9 (The Gambia) to 38.2% (Swaziland)
- Exceeds 20% in Zimbabwe, Zambia, South Africa, Botswana, Swaziland, Lesotho and Namibia
- Exceeds 10% in Central Africa Republic, Malawi and Mozambique

HIV Burden

- Worldwide an estimated 33 million people are living with HIV.
- Since the beginning of the HIV epidemic in 1981, 25 million people have died of AIDS globally.
- Every day, there are 7 400 new HIV infections, 96% of which are in the low-and middle-income countries.
- Sub-Saharan Africa remains the region most heavily affected by HIV, accounting for 67% of all people living with HIV and for 75% of AIDS deaths in 2007.
- Recent evidence shows that HIV is decreasing in some heavily affected countries such as Kenya, Rwanda, Uganda and Zimbabwe.
- SEAR is the second-most affected region in the world with an estimated 3.6 million people living with HIV (PLHIV); of these, 37% are women.
- resulting in a stabilization of the global epidemic (Fig. 1).

**Fig. 1: Estimated number of people living with HIV and adult HIV prevalence
Global HIV epidemic, 1990-2007**



Source: WHO-Regional Office for South-East Asia

Global summary of AIDS epidemic, 2008

Number of people living with HIV in 2008	Total	33.4 million
	Adults	31.3 million
	Women (aged ≥ 15)	15.7 million
People newly infected with HIV in 2008	Total	2.7 million
	Adults	2.3 million
AIDS-related deaths in 2008	Total	2.0 million
	Adults	1.7 million

Source: UNAIDS Joint United Nations Programme on HIV/AIDS

HIV Epidemic – Deaths 2007

	Adults and children	% of Global deaths
Global	2 000 000	
SSA	1 500 000	75%
East Asia	40 000	2%
Western + Central Europe	9 600	0.5%
S/SE Asia	340 000	17%
N. America	9100 – 54 000	0.4% - 2.7%

Cervical cancer continues to be a major burden in most developing countries

- 493,000 new cases
- 1.4 million prevalent cases
- 273,000 deaths

More than 80% of world burden

Source: GLOBOCAN 2002

Cervical cancer

	2002				2025			
	Incidence		Mortality		Incidence		Mortality	
	Number	Rates	Number	Rates	Number	Rates	Number	Rates
World	493 243	16.02	273 505	8.88	756 043	19.30	438 884	11.20
More developed countries	83 437	13.60	39 512	6.44	93 897	14.70	49 567	7.76
Less developed countries	409 404	16.60	233 776	9.48	702 626	21.42	419 474	12.79
Sub Saharan Africa	70 723	21.69	55 082	16.88	119 265	23.08	93 043	18.01

Ferlay et al., GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. Lyon: IARC Press; 2004 [IARC CancerBase No. 5. version 2.0]

- Evidence-based cervical cancer screening strategies in HIV positive women are still being investigated
- Evidence to date suggests that in HIV positive women:
 - HPV expression is more common
 - Persistent HPV infection more common
 - Women are more likely to be infected by multiple types of HPV
 - Progression to SIL and cancer is faster and occurs at younger ages than in HIV-negative women
- Overall, HIV patients 4-5x more likely than uninfected women to develop CIN (cervical intraepithelial neoplasia)
 - Low cumulative incidence of LSIL among HIV-and HIV+ women with CD4>500
 - Heard et al (Antiviral Therapy, 2006) showed incidentSIL not related to CD4 counts, but could not exclude positive effect of HAART
 - When CD4>350, incidence of SIL in HIV+ patients with previously normal cytology on HAART and not onHAART is similar (Siera et al, J of Antimicrobial ChemoTx, 2008)

Invasive cervical cancer in HIV infected women

- Increased risk of Cx Ca in HIV infected women, particularly in those aged 20-34 years
- Disease is characterized by advanced stages at presentation
- Metastasis in unusual locations
- Poor response to treatment
- Higher recurrence rate
- Shorter interval to death

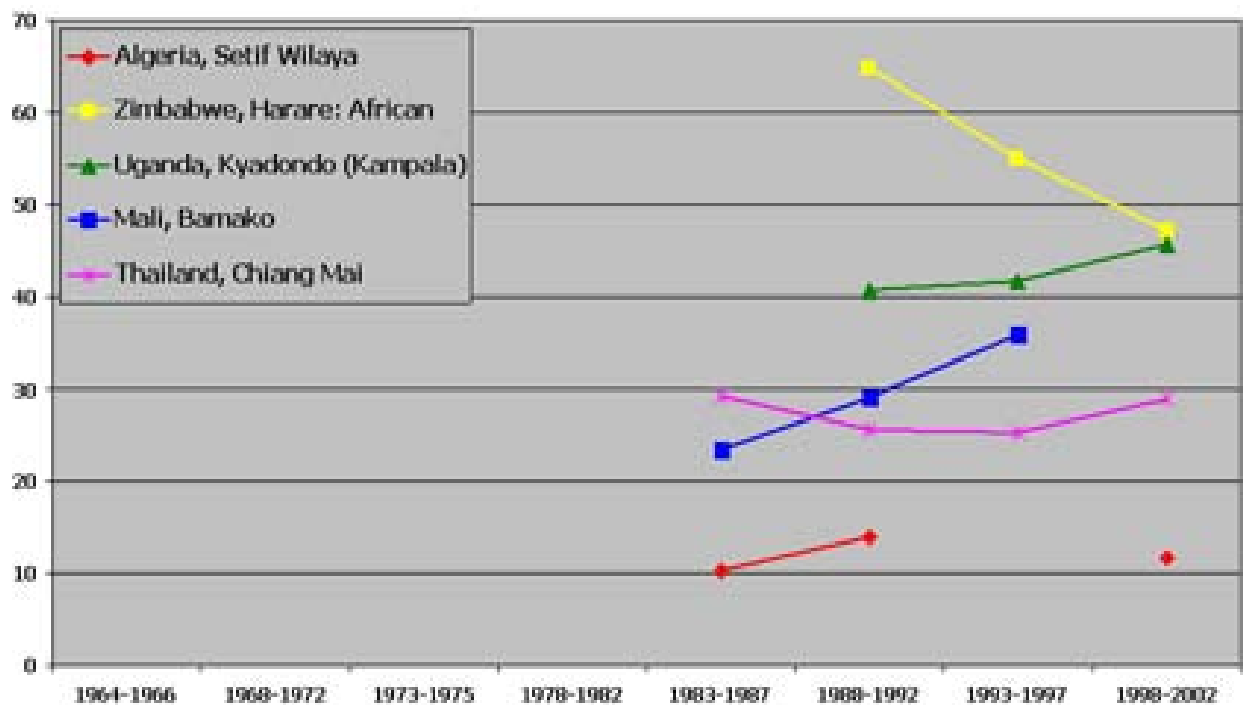
Cervical Cancer as an AIDS defining illness

- Coexistence of HIV and pre-invasive cervical neoplasia is more common than that of HIV and invasive cancer
- However, a large proportion of women have invasive
- cervical cancer as their initial AIDS defining illness
- Maiman et al., 1997: cervical cancer was 55% of AIDS-related cancers in women
 - Women with cervical cancer in study had higher CD4 counts than women with other malignancies
 - Diagnosis of cancer was more likely to precede diagnosis of HIV (possibly 2/2 aggressive screening?)
 - Cause of death in these patients was attributed to cervical cancer rather than other manifestations of HIV infection.

Prevalence of HPV 16/18 in cases of cervical cancer in sub-Saharan Africa

- The prevalence among women with cervical cancer does not appear to differ by HIV status
- 69.2% of 1605 HIV-negative cases and 63.3% of 79 HIV-positive cases had HPV 16/18

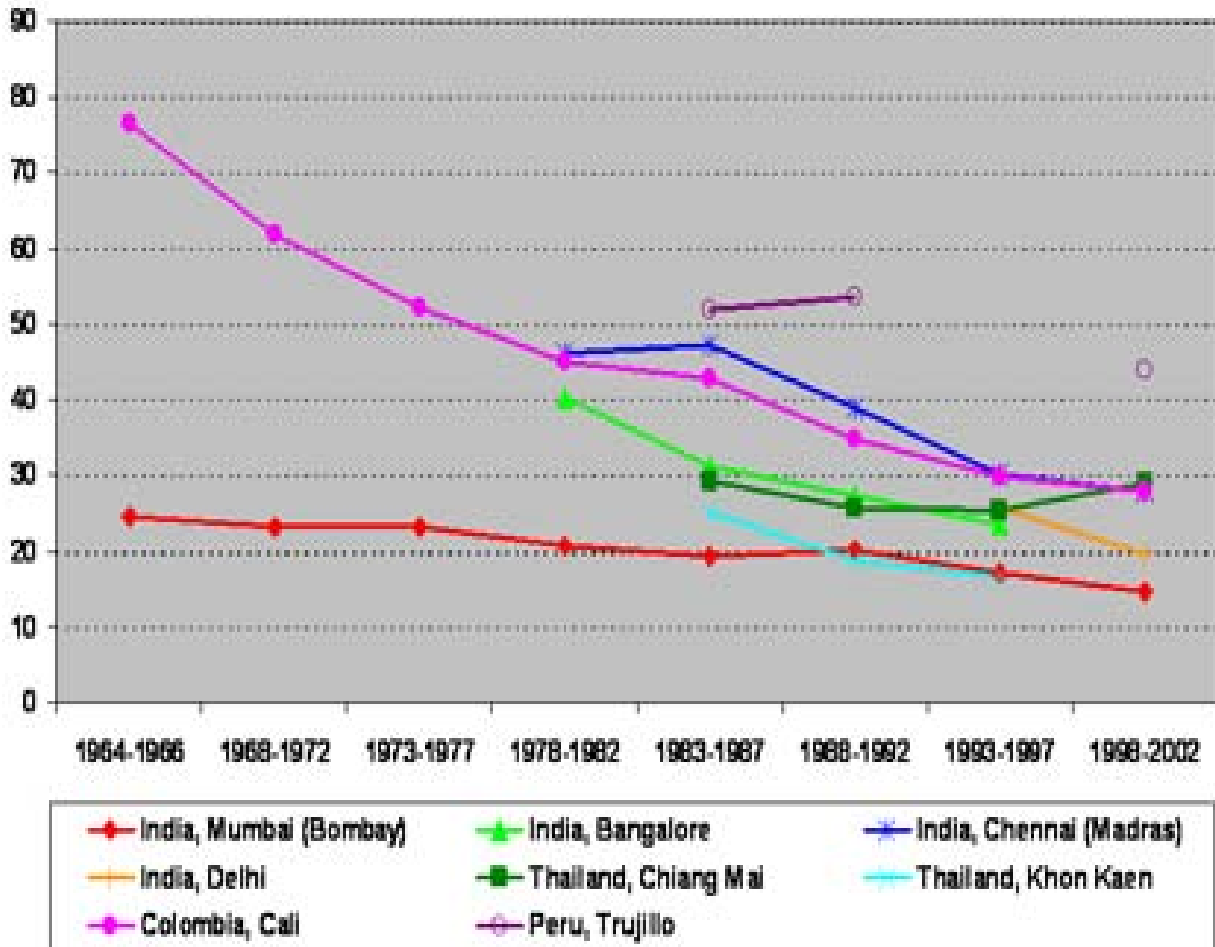
Incidence trends cervical cancer



-Parkin et al., Cancer Incidence in Five Continents, Vol. I to VII. IARC CancerBase No. 7, Lyon, 2005.

-Curado et al., Cancer Incidence in Five Continents, Vol. IX. IARC Scientific Publications No. 160, Lyon, 2007.

Trends in Incidence in Cervix cancer (ASR world)



-Parkin et al., Cancer Incidence in Five Continents, Vol. I to VII. IARC CancerBase No. 7, Lyon, 2005.

-Curado et al., Cancer Incidence in Five Continents, Vol. IX. IARC Scientific Publications No. 160, Lyon, 2007.

Results from a cohort study of 400 HIV-infected women in Cape Town, South Africa

- To study the natural history of infection of the cervix with HPV and of cervical cancer precursors over a 36-month period in a group women infected with HIV-1
- All women underwent Pap, HC II, colposcopy and biopsy of AW lesions, CD4 count, at 6 months apart
- Viral load done at baseline and 18 months post enrolment
- Roche linear array testing for HPV types at baseline and 18 months
- At baseline 55% ASCUS + on Pap smear, 68% HC II positive, median viral load 21,000

- CD 4 count <200: 40%; >500: 14%
- Infected with more than 1 HPV type: 73%

Denny et al., Obstet Gynecol. 2008;111(6):1380-7.

Baseline characteristics between women retained alive in the cohort and women who died

	Retained in Cohort to 36 months (n = 216)	Died (n = 87)	P-value
Mean age	28	29	0.68
Sexually active	165 (76%)	54 (6%)	0.01
HPV +	143 (66%)	67 (77%)	0.05
Median CD4 count	280	98	<0.001
Median Viral load	9000	97 000	<0.001
HSIL cytology	24 (11%)	17 (20%)	<0.001

Denny et al., Obstet Gynecol. 2008;111(6):1380-7.

Incidence, clearance and persistence

- Of women HPV negative at baseline, 22% developed HR-HPV infection by 6 months (n = 90) strongly correlated with low CD4
- Clearance of HPV infection observed in 6% of those women who were positive i.e., 94% infections persisted
- Of women with LSIL on Pap, 11% regressed over 18 months
- Of women with HSIL on Pap, 27% regressed to either LSIL or normal
- Normal/ASCUS progressed to LSIL or HSIL in 17% of cases
- LSIL progressed to HSIL in 4%
- There were no cancers

Denny et al., Obstet Gynecol. 2008;111(6):1380-7.

Predictors of HPV positivity

	HPV-positive (n = 269)	HPV-negative (n =128)	P-value
Mean age	29.1	29.8	0.32
Sexually active	203 (75%)	94 (73%)	0.71
Ever smoked	32 (12%)	15 (12%)	0.98
Median CD4 count	213	335	<0.001
Median Viral Load	33 000	9250	<0.001

Denny et al., Obstet Gynecol. 2008;111(6):1380-7.

Conclusions

- In this cohort of relatively young, untreated HIV-positive women
- High prevalence of HR-HPV infection
-
- 94% of women have persistent HPV infection
- Incident HPV infection occurred in 42% of women who were HPV negative at baseline
- 35% have a baseline cytological diagnosis of LGSIL and 13% HGSIL

Denny et al., Obstet Gynecol. 2008;111(6):1380-7.

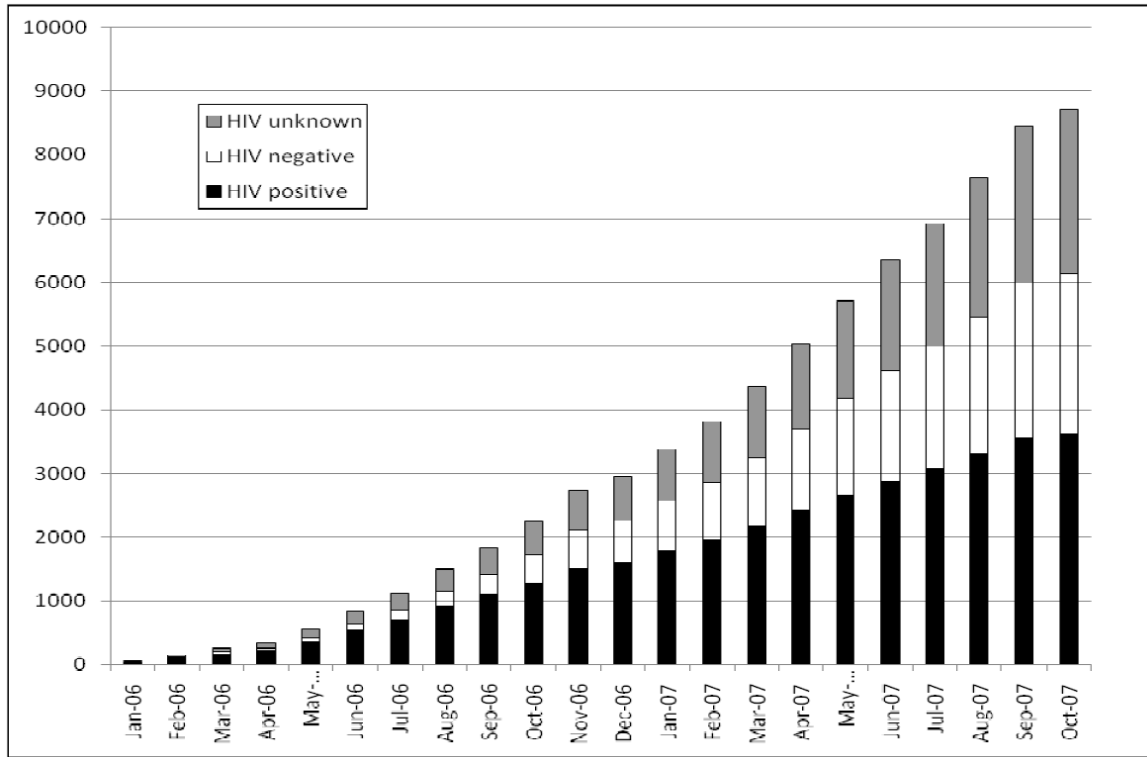
Implementation of a “see and treat” cervical cancer prevention program linked to HIV care in Zambia

- 10 sites in Lusaka
- 4 sites in neighboring districts
- Modern out-patient evaluation center
- 15 nurses with specialized certification
- 30 peer educators
- Database for health records
- Quality assurance program

Pfaender et al., Gynecol Oncol 2008;110(3):402-7 Mwanahamuntu et al., AIDS2009;23(6)N1-N5

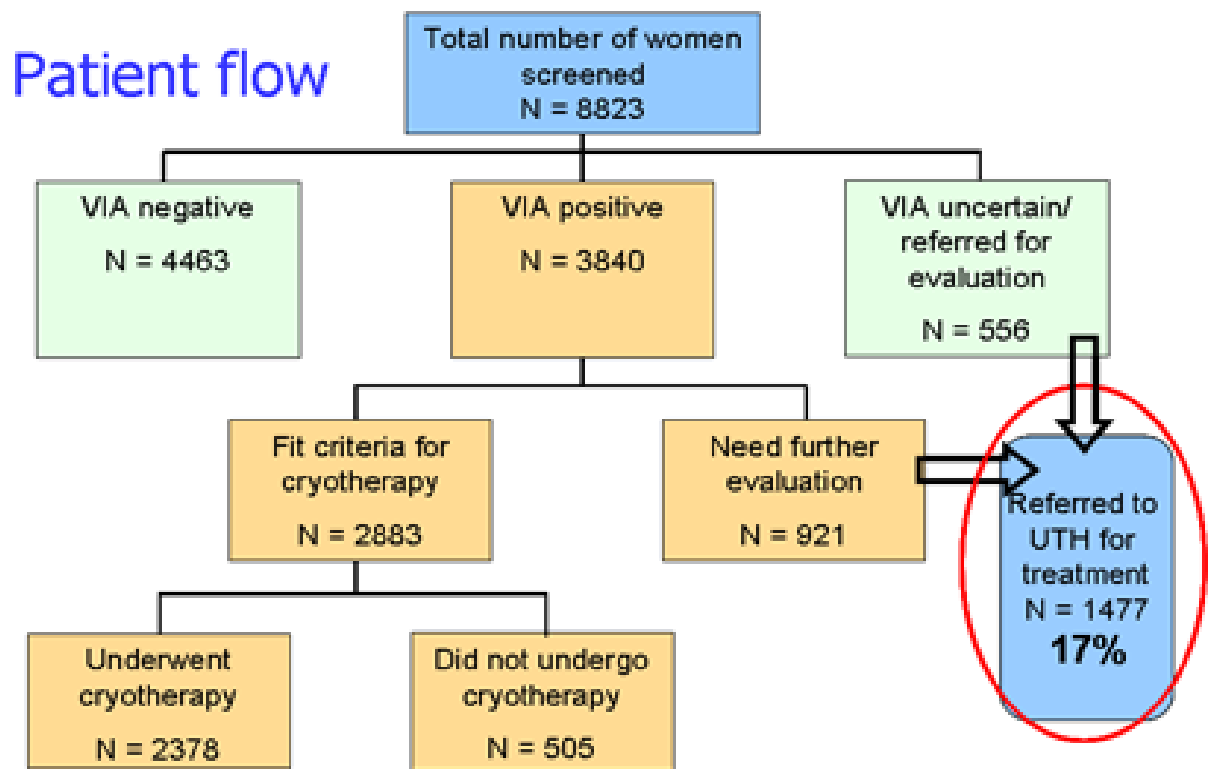
Implementation of a “see and treat” cervical cancer prevention program linked to HIV care in Zambia

Cumulative enrollment (per month) in the cervical cancer prevention program between January 2006 and mid-October 2007 by HIV-serostatus



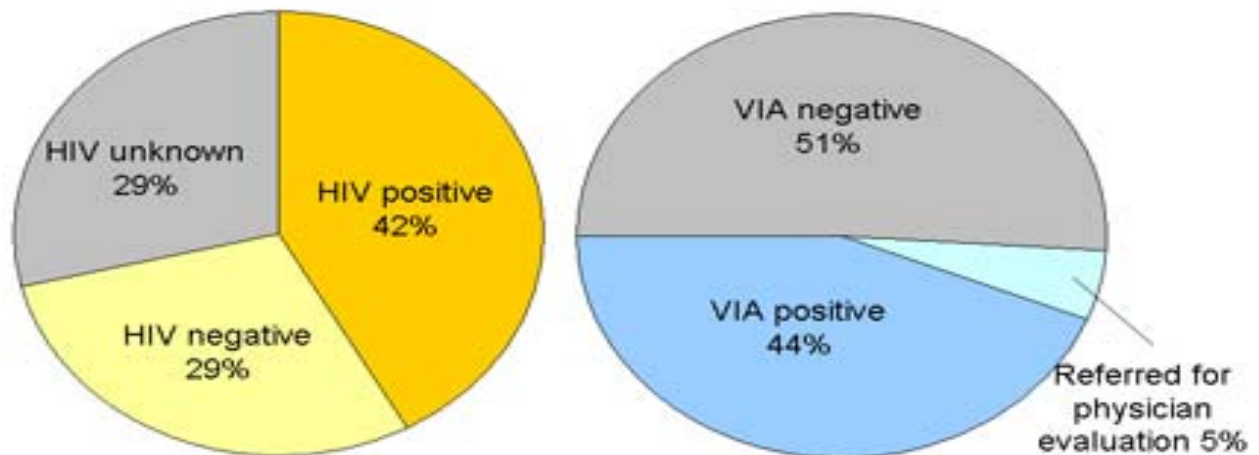
-Pfaender et al., Gynecol Oncol 2008;110(3):402-7 -Mwanahamuntu et al., AIDS2009;23(6)N1-N5

Implementation of a “see and treat”cervical cancer prevention



-Pfaender et al., Gynecol Oncol 2008;110(3):402-7 -Mwanahamuntu et al., AIDS2009;23(6)N1-N5

Implementation of a “see and treat”cervical cancer prevention
HIV-status and VIA-status of women screened

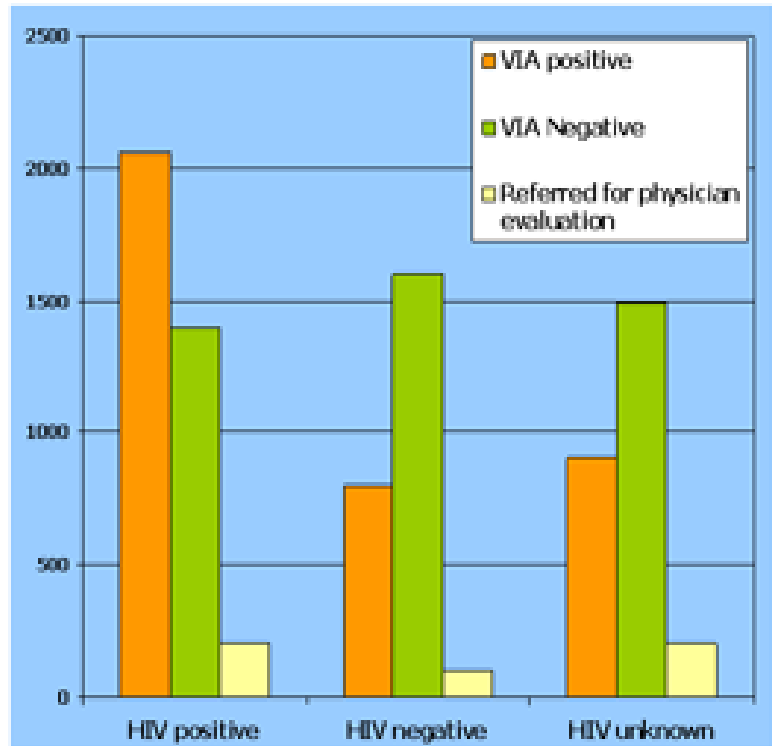


-Pfaender et al., Gynecol Oncol 2008;110(3):402-7 -Mwanahamuntu et al., AIDS2009;23(6)N1-N5

**Implementation of a “see and treat” cervical cancer prevention
VIA results by HIV serostatus**

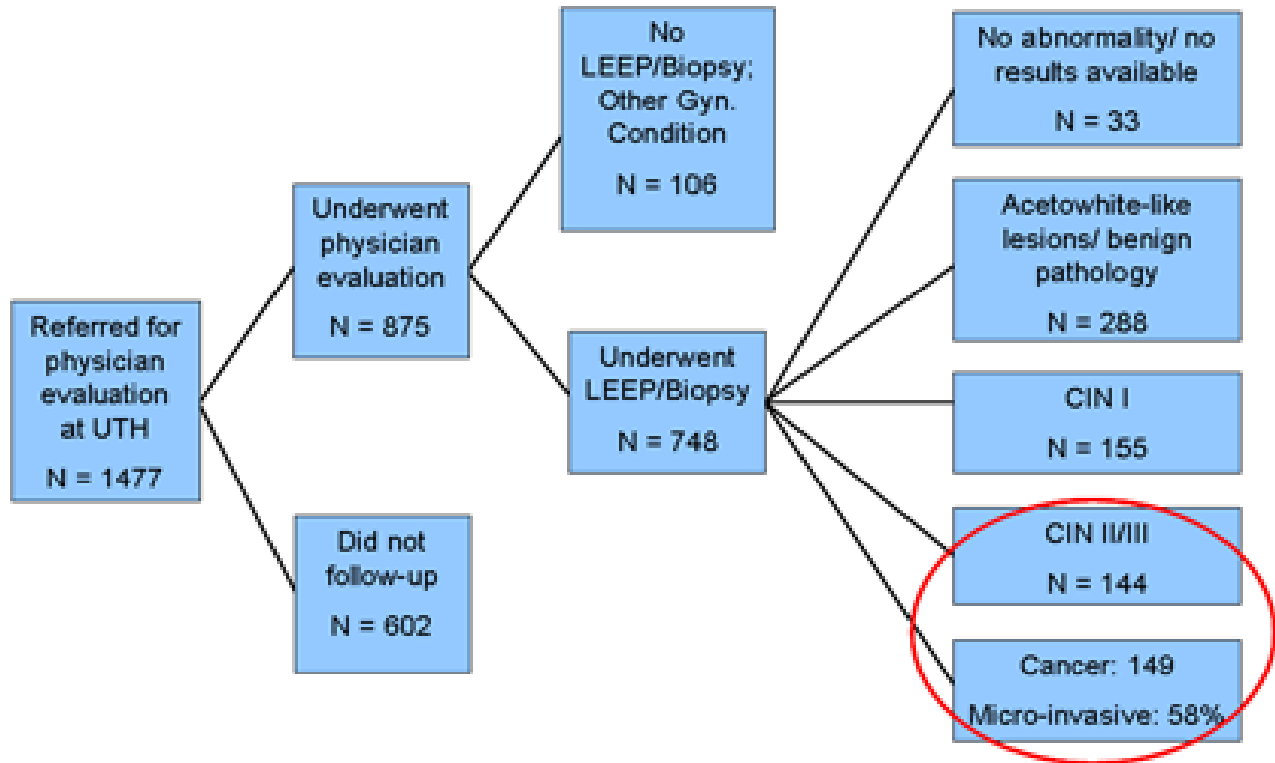
**Proportion of
VIA-positivity (N = 8823)**

- Overall: 44%
- By HIV - serostatus
 - HIV - positive 56%
 - HIV - negative 34%
 - HIV - unknown 35%



- Pfaender *et al.*, *Gynecol Oncol* 2008;110(3):402-7
- Mwanahamuntu *et al.*, *AIDS* 2009;23(6):N1-N5

Implementation of a “see and treat” cervical cancer prevention program linked to HIV care in Zambia



- Pfaender *et al.*, Gynecol Oncol 2008;110(3):402-7
- Mwanahamuntu *et al.*, AIDS 2009;23(6):N1-N5

Effect of HIV infection on treatment outcomes for CIN 2-3 lesions

	HIV + (N = 109)	HIV – (N = 38)
Cure rate of cryotherapy	59.5%	84.2%
LEEP	86%	100%

Chirenje *et al.*, J Low Genit Tract Dis. 2003;7(1):16-21

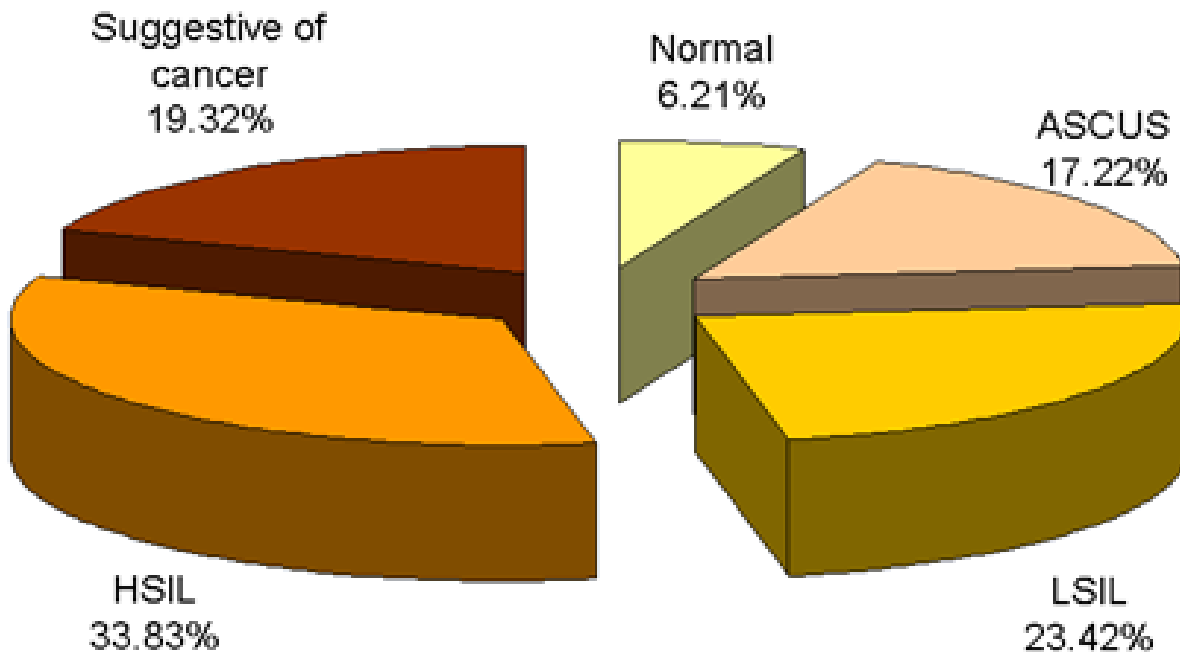
Outcome of LEEP in the treatment of CIN in HIV-infected women in South Africa: frequency of positive cut margins in LEEP specimens

- 70 of 418 (17%) HIV negative women
- 60 of 174 (25%) HIV positive women with no ART Rx
- 102 of 186 (53%) HIV positive women on ART Rx

Pap smear screening in HIV positive women

- Cytology alone as a screening tool is controversial
- Some studies report a low sensitivity for the detection of cytological abnormalities
- Some studies are more reassuring
- 20-60% of Pap smears in HIV-infected women are abnormal
- 15-40% CIN, mostly low grade
- 10-12 times higher abnormalities than HIV negative women
- Increased rate of progression
- Would initially do every 6 months, then annually after two normal Pap smears, unless CD 4 count is below 200
- LBC decreases inadequate smears and one can perform HPV testing using the LBC specimen

**Implementation of a “see and treat” cervical cancer prevention program linked to HIV care in Zambia
Cytology: 150 HIV-infected women in Lusaka**



- Cervical cytology: 2 Pap smears 6 months apart after initial HIV diagnosis
 - if both normal: annual screening
- 2 consecutive normal cytological screenings, annual follow-up including thorough visual examination of anus, vulva, vagina, cervix (in women with CD4>500)
- In those with lower CD4 counts or abnormal findings, recommendation for Pap at 6 months with HPV testing

HPV testing for screening HIV-infected women

Abnormal Pap—now what? (HIV+)

- COLPOSCOPY for evaluation of ALL abnormal cytology screening!!!
(best to have a low threshold for colpo)

Management: Low-grade lesions

- LSIL = CIN 1 = mild dysplasia
- LSIL a cytologic diagnosis, CIN/dysplasia are histologic diagnoses
- HIV-women: regression common (>70%)
- monitor at 6-12 month intervals by serial Pap
- If negative HPV — 2 negative paps at 6-month intervals, then annual Pap
- Or colpo and repeat cytology at 12 months
- Lesions that persist after 1-2 years or progress should be treated
- HIV+ women: CIN 1 regression in approx 33%
- Risk of progression to CIN 2 or 3 not as clear
- HIV +: After colpo, re-Pap after 3 months
- If colpo is satisfactory, excision or ablative modalities may be appropriate for treatment

HPV vaccine in HIV patients?

- Issues to be clarified:
 - HPV vaccine is not contraindicated in HIV patients (ACOG practice bulletin)
 - Safety
 - Greatest benefit would be in young adolescents with HIV (prior to HPV infection)
 - Whether there are enough numbers of HIV+ individuals who are not already HPV infected (for vaccine efficacy)
 - Can HIV+ patients mount and maintain protective antibody titers against HPV?
 - If only women are vaccinated, MSM may serve as pockets of persistence of transmission

HPV Vaccination to prevent cervical cancer in HIV-positive women

- The efficacy of current vaccines against HPV16 and 18 to prevent ICC is likely to be similar in HIV-positive and HIV-negative women
 - Provided vaccination is administered before sexual debut
 - The effect of vaccination on HIV viral load and CD4 counts need to be addressed
-
- Prevention for cervical neoplasia in HIV-infected women is a challenging task
 - Currently available screening tools have limitations
 - VIA screening the most feasible option in impoverished settings
 - The effect of HAART therapy on cervical cancer incidence is not clear