FACULTY OF HEALTH SCIENCES

Western Cape Government

HPV Screening, Triage and HIV Infection

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Cancer in 2012– Global Perspective*

- 14.1 million new incident cases of cancer
- 8.2 million deaths
- 32.6 million living with cancer (within 5 years of diagnosis)
- Of these majority occurred in LMICs
  - 8 million new cancers (56%)
  - 5.3 million of the deaths from cancer (65%)
  - 15.6 million of the 5 year prevalent cases (48%)

*www.globocan.iarc.fr/

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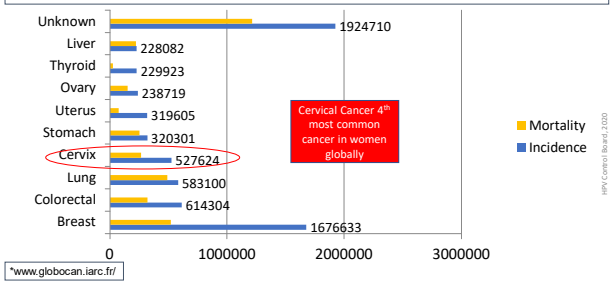
Top Ten Cancers in Women Globally – Globocan data 2012*



*www.globocan.iarc.fr/

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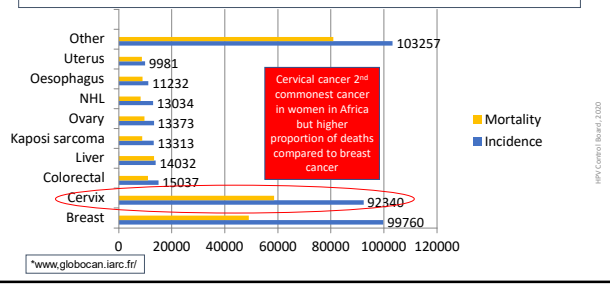
Top Ten Cancers in Women in Africa, Globocan 2012*



*www.globocan.iarc.fr/

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HIV and Cervical Cancer

- Studies have shown that among HIV positive women there is a consistently higher incidence of*:
  - HPV infection
  - Persistent HPV infection with high risk types
  - Infection with multiple types HPV
  - Cervical cancer precursors (CIN or SIL)
  - Greater failure rate of treatment
  - Cervical cancer
- Invasive cancer of the cervix proclaimed an AIDS-defining illness in 1993 (CDC)

*Smith-McCune, K.K. et al. PLoS One, 2010. 5(4): p. e10094, Averbach, S.H. et al. AIDS, 2010. 24(7): p. 1035-42, Low, A.J. et al. BMC Infect Dis. 11: 20 – 26, Veldhuijzen, N.J. et al. AIDS, 2010. 24(14): p. 2289-92,Auvert, B. et al. Infect Dis Obstet Gynecol, 2011: p. 692012

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Human papillomavirus (HPV) related genital disease in the immuno-compromised host*

- Immune status has a significant impact on expression of HPV disease and response to treatment
- Reduced cytotoxic T-lymphocyte reactivity to HPV oncoproteins E6 and E7 leads to impaired ability to clear HPV
- Organ transplant patients and patients with HIV/AIDS suffer from increased rates of HPV infection with increased severity and duration of disease
- These patients are frequently infected with multiple HPV types and have been found to have a higher prevalence of HR HPV-16

*Gormley et al; J Am Acad Dermatol 2012; 66 (6) 2012; 867.e1-867.e14)

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Global Estimates of HIV for Adults and Children 2019*

- People newly infected with HIV 1.7 million
- People living with HIV 38 million
  - 36.2 million adults
  - 1.8 million children (0 - 14 years)
- Deaths due to AIDS related illnesses 690 000
- 81% of all people living with HIV knew their status and about 7.1 million did not know they were living with HIV
- Access to ART 25,4 million
- Since start of epidemic 75.7 million infected and 32.7 million have died from AIDS-related illnesses

* Source: www.unaids.org

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Global HIV & AIDs statistics – 2019*

- 2009: 6.4 million people accessed ART and this increased to 25.4 million in 2019
- 85% of pregnant women living with HIV have access to ART
- New HIV infections have been reduced by 40% since the peak in 1998
- In 2019 there were around 1.7 million people newly infected with HIV compared to 2.8 million in 1998
- On a weekly basis 5500 women aged 15 – 24 years become infected with HIV and in SSA 5/6 new infections occur in girls aged 15 – 19 years
- TB remains leading cause of death among people living with HIV (1 in 3 AIDS-related deaths)

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HPV Prevalence In HIV positive Women with Normal cytology*

Region	Number of Women	HPV prevalence
Africa	2986	1692 (56.6%)
Asia	2523	636 (25.2%)
Europe	2137	591 (27.6%)
North America	2427	821 (33.8%)
South/Central America	1666	1058 (63.5%)
All regions	11739	4798 (40.8%)

*Clifford et al Clinical Infectious Diseases 2017;64:1228 - 1235

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HPV Prevalence in HIV positive women

- Among 796 cases of invasive cervical cancer, 770 came from Africa of whom 702 (91.2%) were HPV positive
- HPV prevalence among women with LSIL cytology was 85% and in women with HSIL cytology it was 92.2%
- In women with histologically confirmed CIN 3 HPV prevalence was 96%

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Cape Town Screen and Treat Study

- Randomized clinical trial
- 6553 unscreened women 35-65 years in Cape Town, South Africa*
- 14% HIV-positive at baseline
- Comparison of HPV prevalence and CIN
  - 956 HIV-positive vs. 5596 negative women

*Denny et al JAMA 2010

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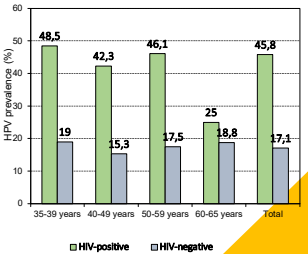
HR-HPV prevalence In HIV-positive and HIV-negative women



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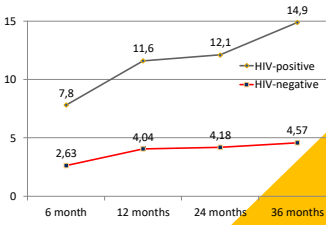
Risk of CIN2+in HIV-positive And HIV-negative women



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HPV-associated disease

- Persistent infection with high-risk types of HPV is a necessary event in the pathogenesis of cervical cancer
- Up to 80% of sexually active persons over the age of 15 will be infected with HPV at some time
- Transmission is by skin to skin contact
- Most infected individuals clear the infection within 8 months and the infection has no clinical consequences
- A minority of infected individuals will demonstrate HPV related disease
  - Genital warts
  - Respiratory papillomatosis
  - Ano-genital invasive disease and/or precursors
  - Head and neck cancers

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Relationship HIV and HPV infection in women seroconverting

- SA Study*
  - 5595 women aged 35 – 65 followed over 36 months
  - 557 HIV positive at enrolment
  - 123 sero-converted during trial
    - Prior to sero-conversion high-risk HPV positive **20.3%**
    - During sero-conversion high-risk HPV positive **23.6%**
    - Post sero-conversion high-risk HPV positive **49.1%**

*Wang et al. J Infectious Diseases 2011:203(4):479 – 86

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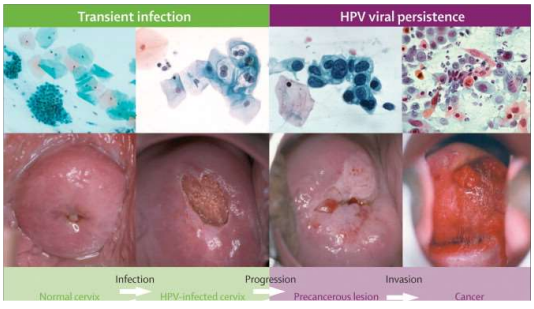

Schiffman et al The Lancet 2007;370(9590):890 - 907

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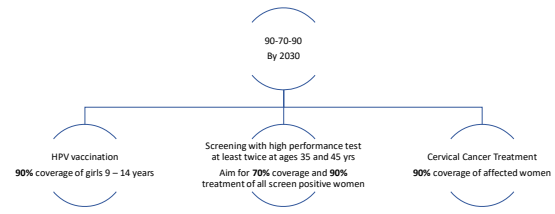
Elimination of Cervical Cancer: WHO Draft Strategy



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Triage of HPV positive women in cervical cancer screening

- Recommended strategies include:
  - HPV genotyping with HPV 16/18 and cytology
  - P16/Ki-67 dual staining cytology
  - Host methylation
  - Viral methylation testing
  - Use of risk thresholds for return to primary screening, repeat testing, referral to colposcopy, immediate treatment

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Modifying HPV DNA testing to optimise specificity*

- WHO has recommended HPV-based screen and treat approach in low resource settings
- The concern however is the relatively low specificity of HPV testing in general and specifically in HIV positive women, which leads to overtreatment
- There are a number of ways of addressing this problem
  - One is to use a triage test in HPV positive women (VIA, Cytology, or additional HPV tests) prior to treatment
  - Our group evaluated using HPV-type restriction and more stringent cut-offs on the Xpert HPV (Cepheid) to define a positive test prior to treatment, in order to optimise specificity

*Kuhn L et al Lancet Glob Health 2020;8:e296 - 304

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About Xpert-HPV assay (Cepheid)

- PCR assay that detects and types 15 types of high-risk HPV DNA
- The different HPV DNA types are grouped into 5 channels:
  - HPV 16
  - HPV 18 and/or 45
  - HPV 31, 33, 35, 52, and/or 58 (P3)
  - HPV 51 and/or 59 (P4)
  - HPV 39, 56, 66 and/or 68 (P5)
- For each channel a cycle threshold (CT) value is generated and values below CT cut-offs are defined as "positive".

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Advantages of Xpert-HPV as POC test

Cartridge is preloaded with all required reagents

No specialized lab skills required

Fully automated real-time PCR instrument Doesn't require "batching"

<1 min of operator "hands-on" time

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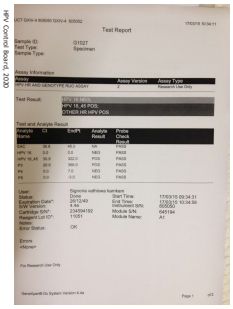

- Real-time PCR for 14 targeted HPV types in 5 channels plus sufficiency control:
- **HPV16;**
- **HPV18 45;**
- **[P3] HPV31, 33, 35, 52, 58;**
- **[P4] HPV51 59;**
- **[P5] HPV39, 56, 66, 68**

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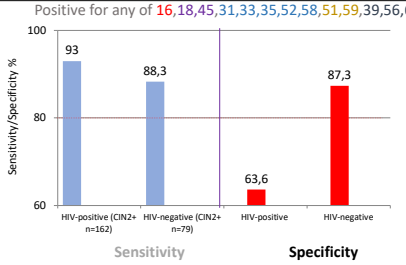
Evaluate Xpert-HPV "as is"

Positive for any of 16,18,45,31,33,35,52,58,51,59,39,56,66,68



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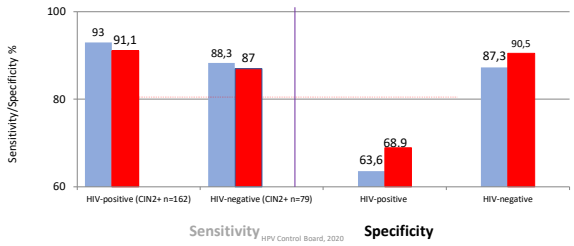
Restrict to specific HPV types

Positive for **16**, **18,45**, **31,33,35,52,58**, ~~51,59,39,56,66,68~~



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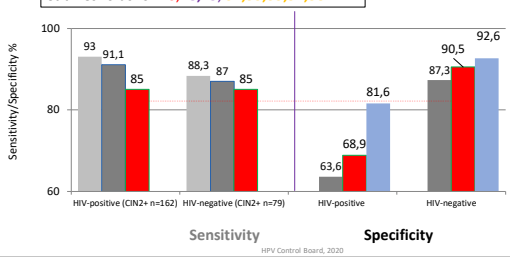
Optimize Ct thresholds for specific HPV channels

Ct thresholds for **16**,**18,45**, **31,33,35,52,58**



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Main findings

- By restricting the result to specific HPV types in the first three channels and by changing the cycle thresholds for defining screen-positive, we attained an *85% sensitivity* for the detection of histologically confirmed HSIL in the whole group
- Specificity for HIV-negative women was 93% and for HIV-positive women was 82%
- The best algorithm optimized **Ct values** in the three channels that detected HPV types **16,18,45,31,33,35,52,58**
- These data showed that by altering the definition of a positive HPV-Expert test, specificity could be significantly increased without lost of sensitivity in both HIV-positive and HIV-negative women
- This algorithm is ideal for low resource settings where a *positive test* can be linked to *immediate/same day treatment*, obviating the need for return visits and reducing lost to follow up

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New Technologies

- Visual Assessment of Cervix is an intrinsic component of cervical cancer screening and takes on different forms:
  - Naked eye inspection of the cervix
  - VIA (with 3 – 5% acetic acid)
  - Colposcopic assessment with acetic acid (with or without histological sampling)

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New Technologies

- Automated Visual Evaluation (AVE)
  - Capitalises on mobile phone technology
  - MobileODT has developed the Enhanced Visual Assessment system (EVA)
  - Device is essentially a cellphone with excellent optical magnification and an enhanced light source
  - Access to internet and software has been added to the phone to augment clinical utility
  - Software enables storage of digital images for record purposes and quality control and the potential to upload images to the cloud-based system
  - The database is able to retain patient information with key clinical information and allow for expert review

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EVA Device

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New Technologies

- The AVE system applies advances in machine-learning methods and artificial intelligence, enabling the system to perform an automated diagnosis based on digital imaging of the cervix
- We plan to evaluate the MobileODT system as an adjunct to assist and *possibly replace* the diagnosis of specialised colposcopy
- To train nurse clinicians to evaluate women participating in screen and treat programmes who are HR – HPV positive
- Utility of AVE system to detect disease in women who have undergone prior ablative therapy due to HPV positivity

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Conclusions

- Molecular testing for detection of high risk HPV DNA is the future
- Issue of most reliable triage will depend on resources available and desired outcome
- Implementation of screen and treat requires more health systems evaluation
- Qualitative research with diverse women to understand barriers and/or acceptance of screen and same day treatment
- How to integrate screen and treat programmes with HPV vaccination
- Critical to success is widespread coverage with high-quality treatment of presumed preinvasive lesions

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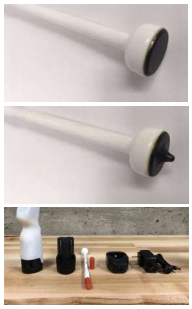
Liger™ Thermocoagulator



- Battery operated
- Rechargeable
- Highly portable
- Reasonably priced

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