Contracpetion in women living with HIV

Human Pappiloma Virus and Cancer

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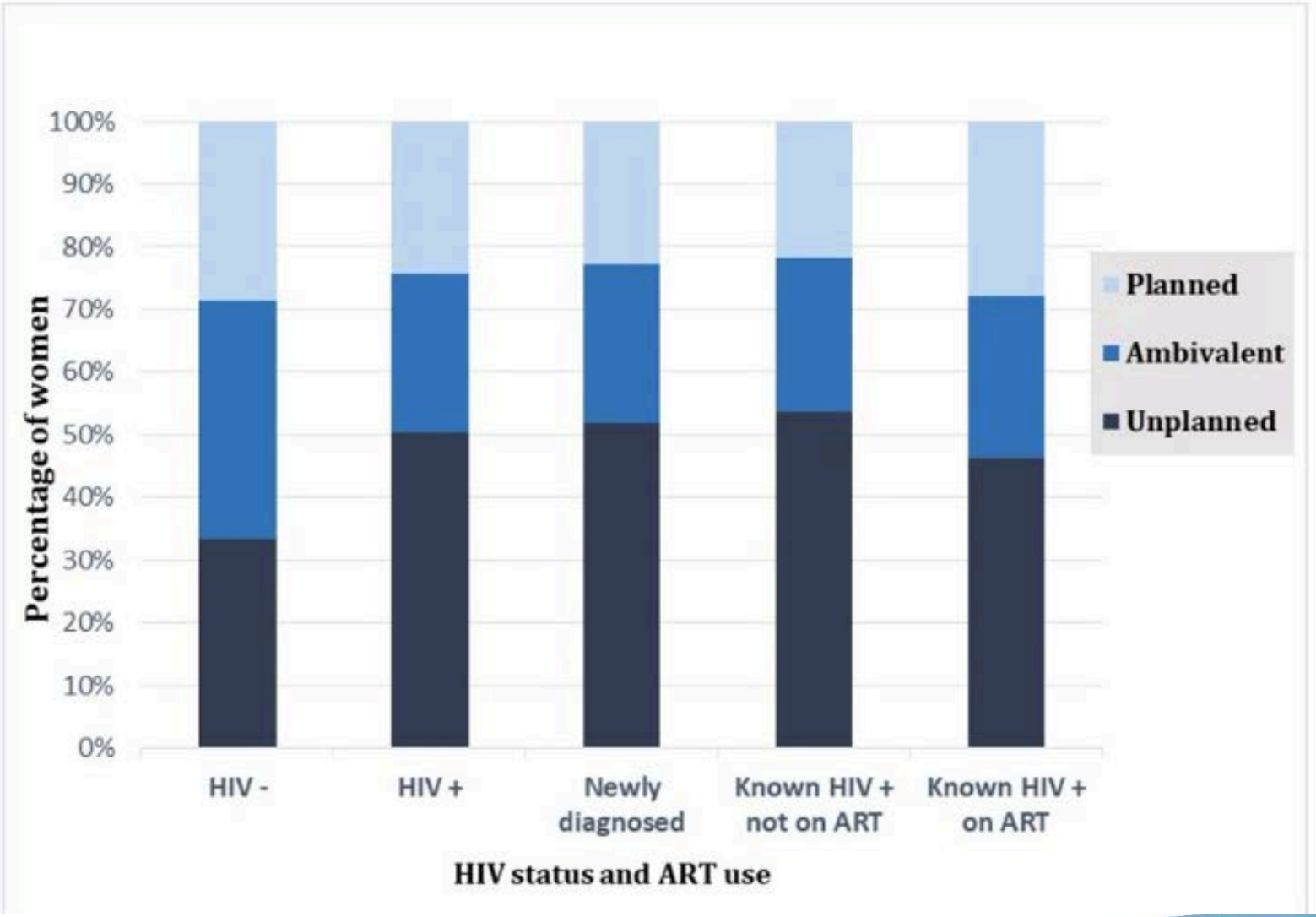
Unplanned pregnancies according to HIV status and ART



Iyun V et al BMJ open 2018

Which is the best contraception after U=U ?

DOI: 10.1111/hiv.12582
HIV Medicine (2018)

ORIGINAL RESEARCH

Neglect of attention to reproductive health in women with HIV infection: contraceptive use and unintended pregnancies in the Swiss HIV Cohort Study

K Aebi-Popp,[1,†] V Mercanti,[2,†] C Voide,[3] J Nemeth,[4] A Cusini,[1] B Jakopp,[5] D Nicca,[6] M Rasi,[7] A Bruno,[8] A Calmy[9,†] and B Martinez de Tejada[2,†] for the Swiss HIV Cohort Study[†]

SWISS HIV COHORT STUDY

Contraception used:

- **Condoms 73.5%**
- Oral hormonal contraception 10.7%
- Intrauterine devices 9.4%
- Unplanned pregnancies 20 %

VIEWPOINT

Journal of Virus Eradication 2017; 3: 90–91

The 'post-condom era' or the urgent need to provide effective contraception for women living with HIV

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After U=U condoms are not necessarily used in stable discordant partnerships
→ which contraceptive ?

Action of hormonal contraception

Effectiveness:

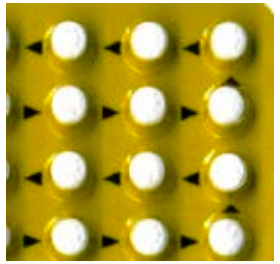
- **Progestin (e.g. Levonorgestrel, Etonogestrel, Norgestimate):** Causes cervical mucus thickening , partly inhibits ovulation

Tolerability:

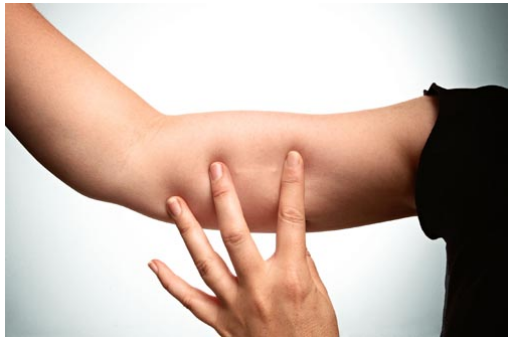
- **Estrogen (Ethinyl estradiol, EE)**: Stabilizes endometrium, inhibits follicle stimulating hormone (FSH) to prevent follicle capture

Pharmacokinetics: Contraceptives are different

- Route of administration: Intrauterine device (IUD), implant, injection, tablet
- Doses and indications are very different



Progestin only



Estrogen and Progestin

Contraceptive failure rates

(rates per 100 episodes of typical use)

	12 months	24 months	36 months
Implant	0.6	1.0	1.1
IUD	1.4	1.9	2.1
Injectable	1.7	3.6	5.5
Pill	5.5	10.8	15.1
Male condom	5.4	13.3	16.0
Withdrawal	13.4	27.4	35.7
Periodic abstinence	13.9	25.8	32.4

Polis et al, Contraception 2016

Challenges for assessment of “real life” drug-drug interactions (DDIs)

- **Unintended pregnancy** as ultimate outcome
- Most studies use only **surrogate measures**
  - Endogenous progesterone or ultrasound to assess ovulation
- Inter- and intra-individual variability in hormone concentrations
- Drug metabolism of hormones is poorly defined: **no pharmakological threshold** for efficacy or toxicity

Nanda et al: systematic review AIDS 2017

DDIs between ART and HC and clincal impact

Estrogens/ progestins metabolized by cytochrome P450 (CYP) enzymes

-Progestins primarily CYP3A4

-Estrogens primarily CYP3A4, CYP2C9 and UGT1A1

- **lower progestin** levels: **may impair effectiveness**
- **higher progestin, lower or higher estrogen levels**:

  consider adverse effects

www.hiv-druginteractions.org

UNIVERSITY OF LIVERPOOL

Contraceptive Treatment Selector

Charts reviewed October 2018. Full information available at www.hiv-druginteractions.org

		ATV/r	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	RAL	ABC	FTC	3TC	F/TAF	E/C/F/TDF
	Ethinylestradiol	↓19%[a]	↓44%[b]	↓42%[b]	↔ ↓[c]	↑22%	↓20%	↑14%	↔	↑3%	↔				↓25%[d]	↓25%[d]
Progestins (COC)	Desogestrel	↑[a,e]	↑[e,f]	↑[e,f]	↓[g]	↓	↓	↔	↔					↔	↑[h]	↑[h]
	Drospirenone	↑[a]	↑[f]	↑[f]	↓[g]	↓						↔	↔	↔	↑[h]	↑[h]
	Gestodene	↑[a]	↑[f]	↑[f]						↔	↔	↔	↔	↔	↑[h]	↑[h]
	Levonorgestrel	↑[a]						↔	↔	↔	↔	↔	↔	↔	↑	↑
	Norethisterone (Norethindrone)	↑[a,i]	↓1		↓[g]	↓5%	↓19%	↓11%	↔	↔	↔	↔	↔	↔	↑[h]	↑[h]
	Norgestimate	↑85%[a]														↑126%[h]
	Norgestrel	↑[a]														↑[h]
Progestins (POP)	Desogestrel	↑														↑
	Levonorgestrel	↑														↑
	Norethisterone (Norethindrone)	↑50%[i]	↑													↑

Colour Legend

- No clinically significant interaction expected.
- These drugs should not be coadministered.
- Potential interaction which may require a dosage adjustment or close monitoring.
- Potential interaction predicted to be of weak intensity or unlikely to impair contraceptive efficacy. I

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	Drospirenone	↑[a]	↑[f]	↑[f]							
	Gestodene	↑[a]	↑[f]	↑[f]							
	Levonorgestrel	↑[a]	↑[f]	↑[f]							
	Norethisterone (Norethindrone)	↑[a,i]	↓14%[g]	↓17%[g]							
	Norgestimate	↑85%[a]	↑[f]	↑[f]							
	Norgestrel	↑[a]	↑[f]	↑[f]							
Progestins (POP)	Desogestrel	↑	↑	↑	↓[g]	↓	↓	↔	↔	↔	↔
	Levonorgestrel	↑	↑	↑	↓[g]	↓	↑	↔	↔	↔	↔
	Norethisterone (Norethindrone)	↑50%[i]	↑50%	↑50%	↓[g]	↓	↓	↔	↔	↔	↔

Boosted PI and combined pill

→lower estrogen levels

- more irregular bleeding
- combined pill with at least 30 µg/l EE

→mostly higher progestin levels

- may have side effects (e.g.edema, nausea, acne)

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	Drospirenone	↑[a]	↑[f]	↑[f]	↓[g]					
	Gestodene	↑[a]	↑[f]	↑[f]	↓[g]					
	Levonorgestrel	↑[a]	↑[f]	↑[f]	↓[g]					
	Norethisterone (Norethindrone)	↑[a,i]	↓14%[g]	↓17%[g]	↓[g]					
	Norgestimate	↑85%[a]	↑[f]	↑[f]	↓64%[g]					
	Norgestrel	↑[a]	↑[f]	↑[f]	↓[g]					
Progestins (POP)	Desogestrel	↑	↑	↑	↓[g]					
	Levonorgestrel	↑	↑	↑	↓[g]					
	Norethisterone (Norethindrone)	↑50%[i]	↑50%	↑50%	↓[g]	↓	↓	↔	↔	↔

Efavirenz
→lower progestin levels

Impact on effectiveness !

(pill, but also implant, patch and vaginal ring)

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Progestins (COC)	D						↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑[h]	↑[h]
	D						↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑[h]	↑[h]
	G						↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑[h]	↑[h]
	L						↑	↔									↑	↑
	N (Norethindrone)	↑	↓14%[c]	↓17%[c]	↓[c]	↓5%	↓19%	↓11									↑[h]	↑[h]
	Norgestimate	↑85%[a]	↑[f]	↑[f]	↓64%[g]	↓	↓	↔									↑126%[h]	↑126%[h]
	Norgestrel	↑[a]	↑[f]	↑[f]	↓[g]	↓	↑29%	↔									↑[h]	↑[h]
Progestins (POP)	Desogestrel	↑	↑	↑	↓[g]	↓	↓	↔									↑	↑
	Levonorgestrel	↑	↑	↑	↓[g]	↓	↑	↔									↑	↑
	Norethisterone (Norethindrone)	↑50%[i]	↑50%	↑50%	↓[g]	↓	↓	↔									↑	↑

Integrase inhibitors and NRTI→ no known DDI with hormons

- PrEP: no interaction

E/C/F/TAF and E/C/F/TDF

→ lower estrogen levels

- may cause irregular bleeding
- give at least EE 30 µg/l

→ higher norgestimate levels

- may cause side effects (e.g.edema, nausea, acne)

www.hv-druginteractions.org

Contraceptive Treatment Selector

Charts reviewed October 2018. Full information available at www.hiv-druginteractions.org

		ATV/r	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	RAL	ABC	FTC	3TC	TDF	ZDV	E/C/F/TAF	E/C/F/TDF
Progestins (Non-oral)	Etonogestrel (implant)	↑	↑	↑52%	↓63%[k]	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Etonogestrel (CVR)	↑~80%[j]	↑[j]	↑[j]	↓~80%[k]	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑[j]	↑[j]
	Levonorgestrel (IUD)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Levonorgestrel (implant)	↑	↑	↑	↓47%[k]	↓	↑14%	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Medroxy-progesterone (depot)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Norelgestromin (patch)	↑[l]	↑[m]	↑83%[m]	↓[g]	↓												↑[h]
	Norethisterone (Norethindrone) (depot)	↔	↔	↔	↓[g]	↓												↑
Other	Levonorgestrel (EC)	↑[n]	↑[n]	↑[n]	↓58%[o]	↔												↑[n]
	Mifepristone	↑[n]	↑[n]	↑[n]	↓	↓												↑[n]
	Ulipristal	↑[n]	↑[n]	↑[n]	↓[p]	↓[p]												↑[n]

Non-oral- hormonal contraception

- Levonorgestrel intrauterine device: no DDI
- Medoxyprogesteron injectable: no DDI

Emergency contraception:

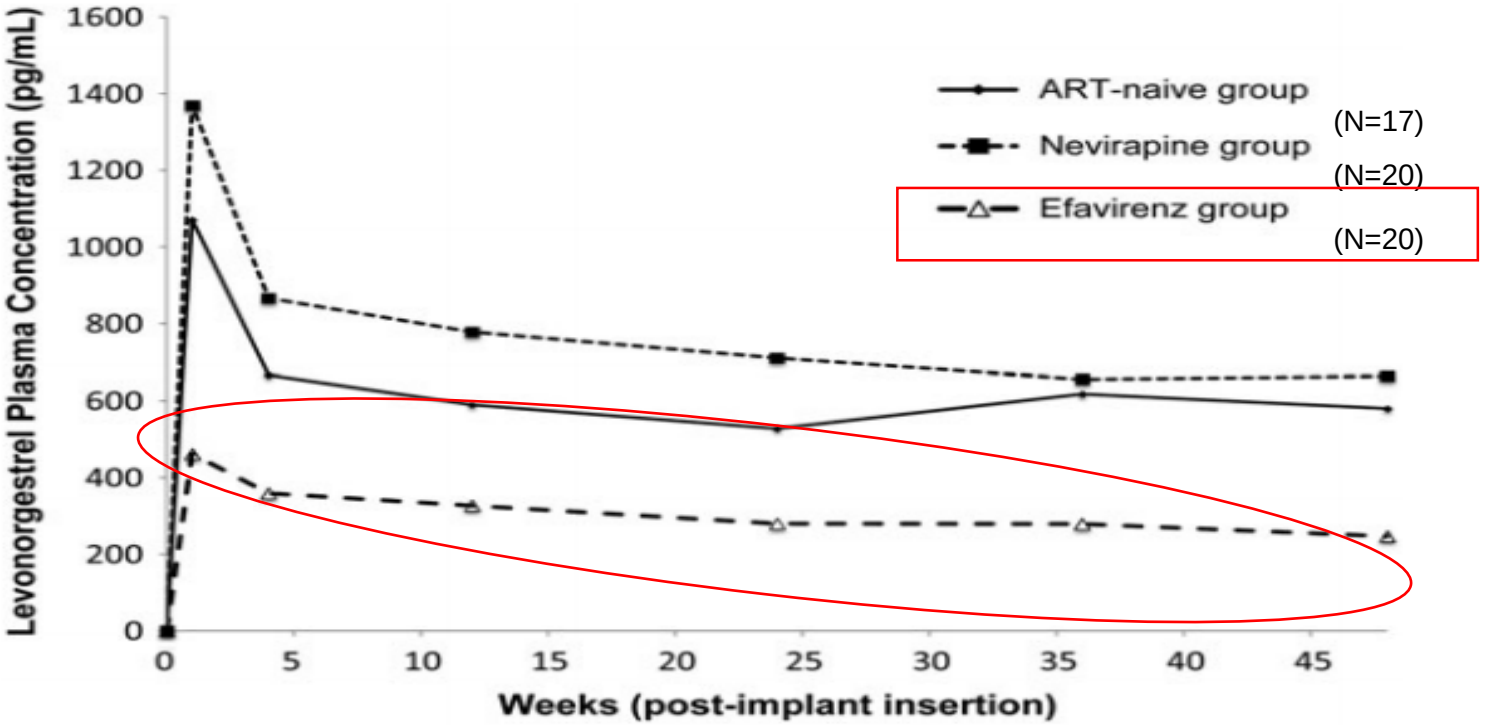
- EFV: lower LNG levels

DDIs: Efavirenz and Levonorgestrel implant

Scarsi KK, et al. Clin Infect Dis 2016;62:675-82

Levonorgestrel implant – LNG levels over 48 weeks post-implant by ART group

LNG Concentration-Time Profile by ART Group



→ # pregnancies (contraceptive failure):

- **EFV**: 3/20 (15%)
- NVP: 0
- ART-naïve: 0

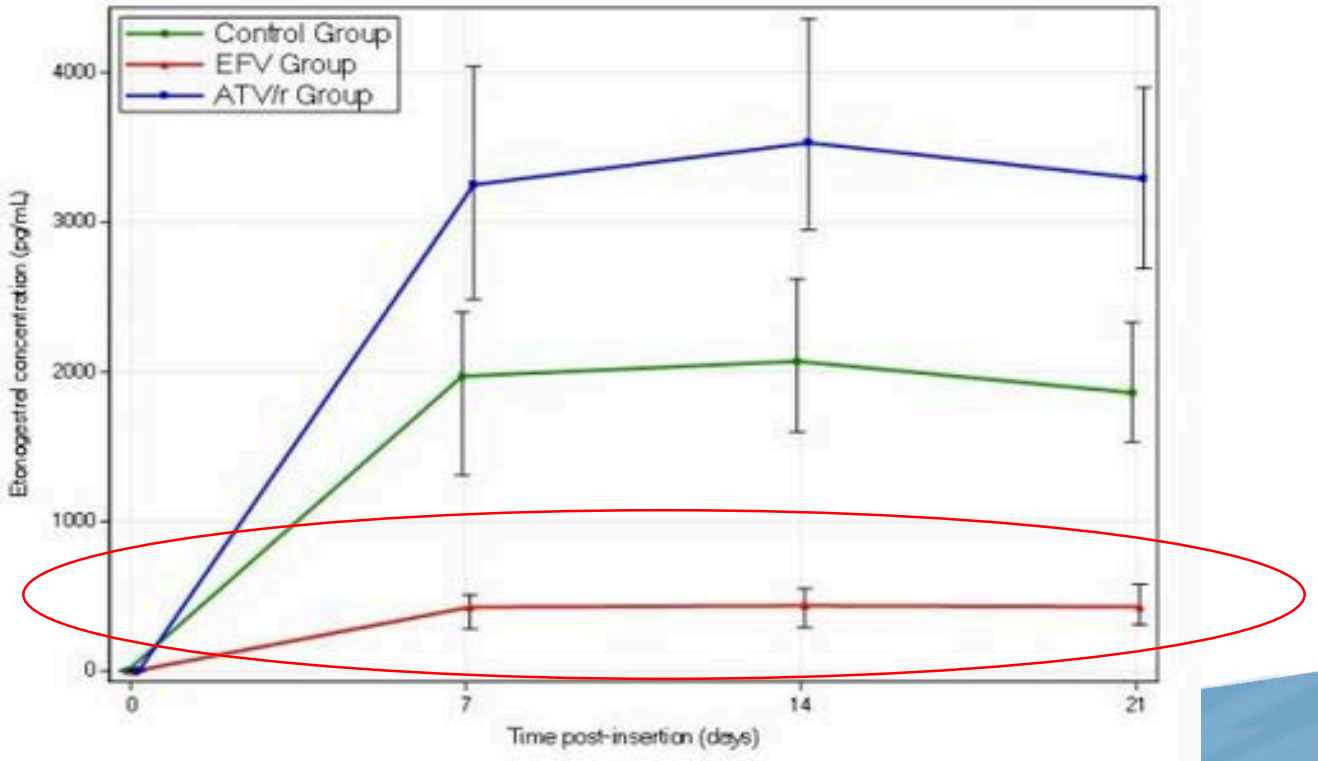
→ EFV group had significantly lower LGN levels by week 1 post implant which persisted over time.

DDIs: Efavirenz and Vaginal Ring Reduced Etonorgestrel levels

Scarsi et al. CROI 2018

- ATZ/r based ART unlikely to impact effectiveness of ring
- EFV based ART likely to decrease effectiveness

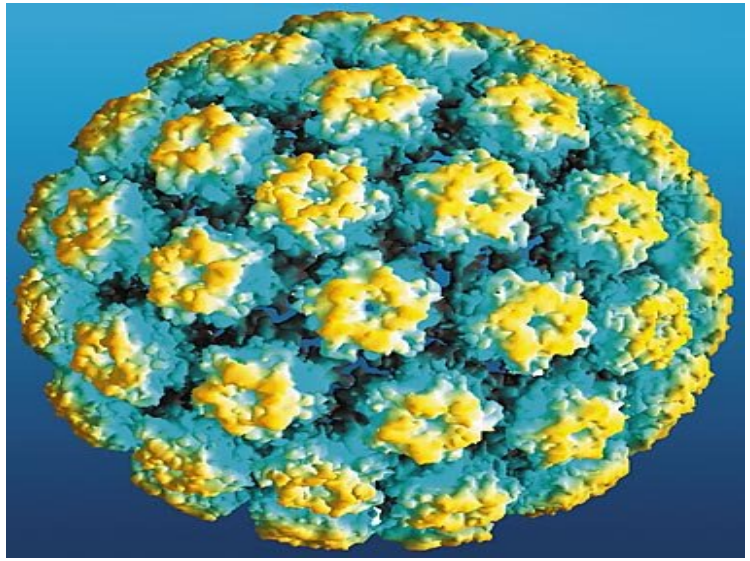
Figure: Median (interquartile range) ENG concentrations (pg/mL) in each group

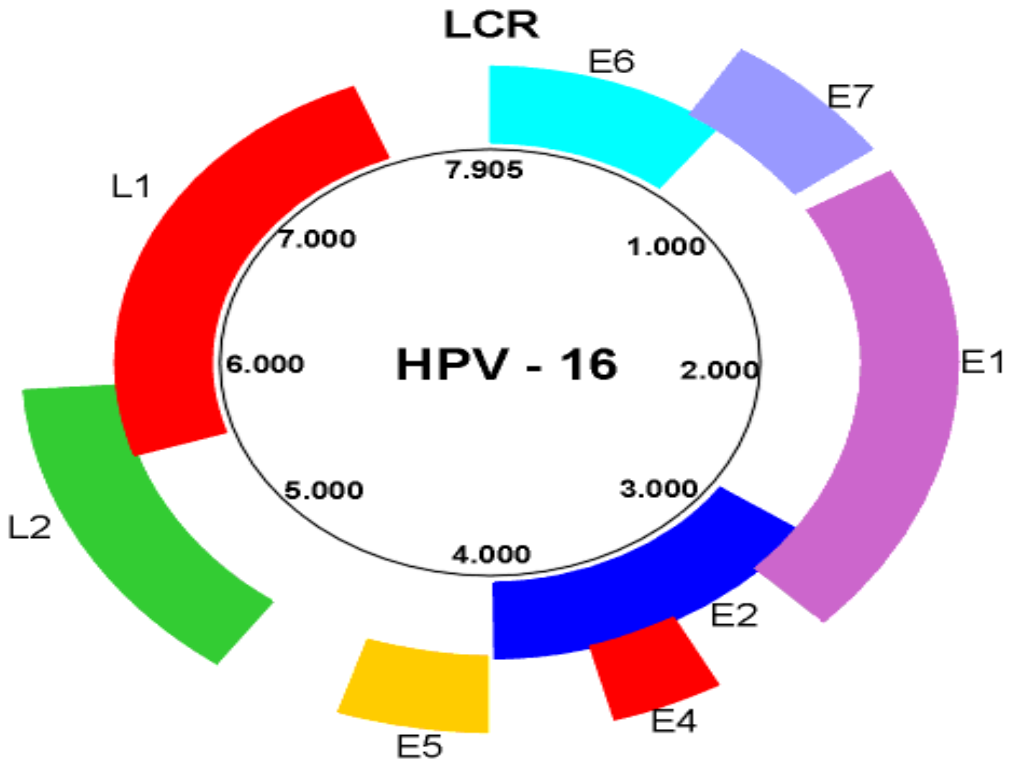


Summary contraceptives and ART

- Most contraceptives are well tolerated and safe in women on cART: Do offer contraceptives !
- EFV based ART decreases contraceptive effectiveness in implant, patch, vaginal ring and COC
- PrEP does not affect hormonal contraceptives effectiveness
- Impact of DDIs according to route of administration: Hormonal IUD is always a good option

HPV: Human PapillomaVirus



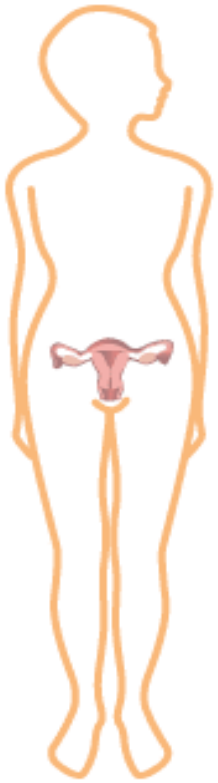


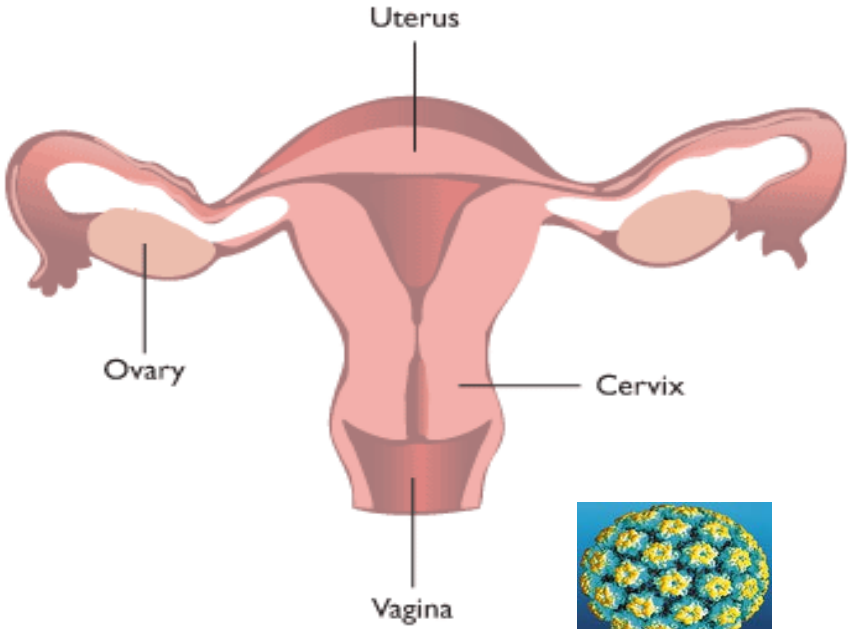
What are the HPV-induced cancers?

ADN HPV

- Cervix 99%
- Anus 84%
- Vagina 70%
- Vulva 40%

- Oro-pharyngal 35%





High risk HPV (HPVHR)

16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68

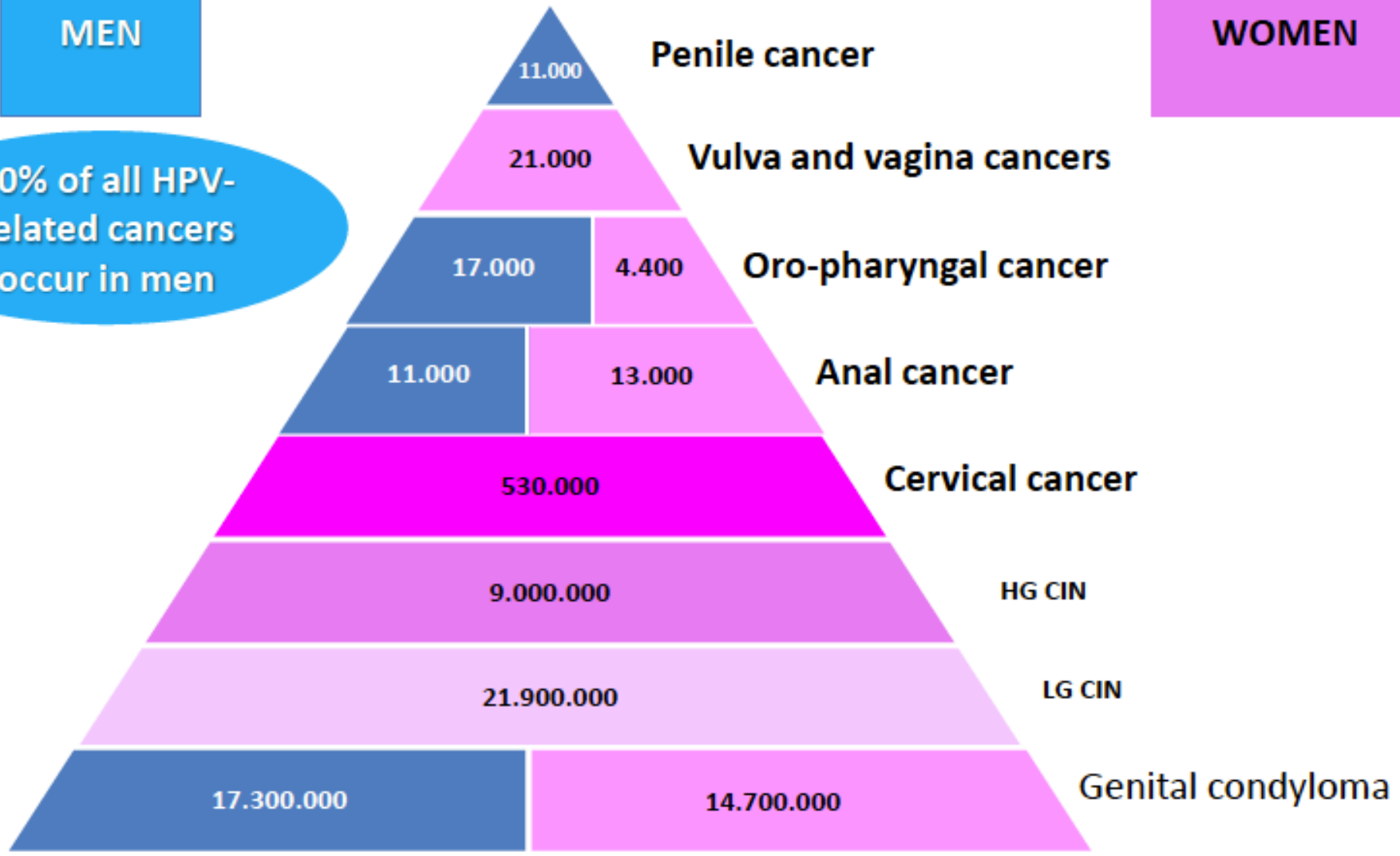
70%

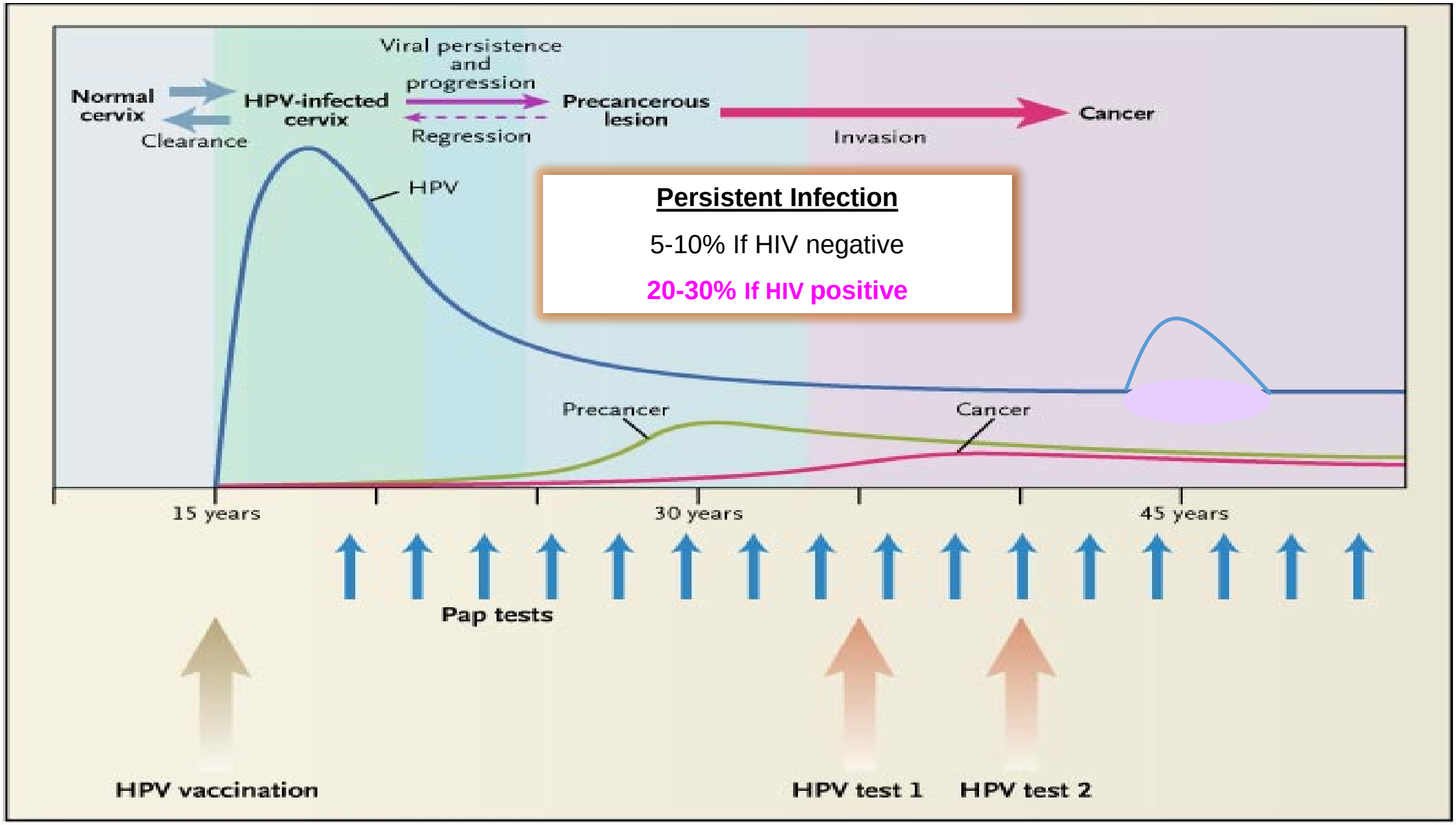
Slide courtesy
Deborah Konopnicki

MEN

WOMEN

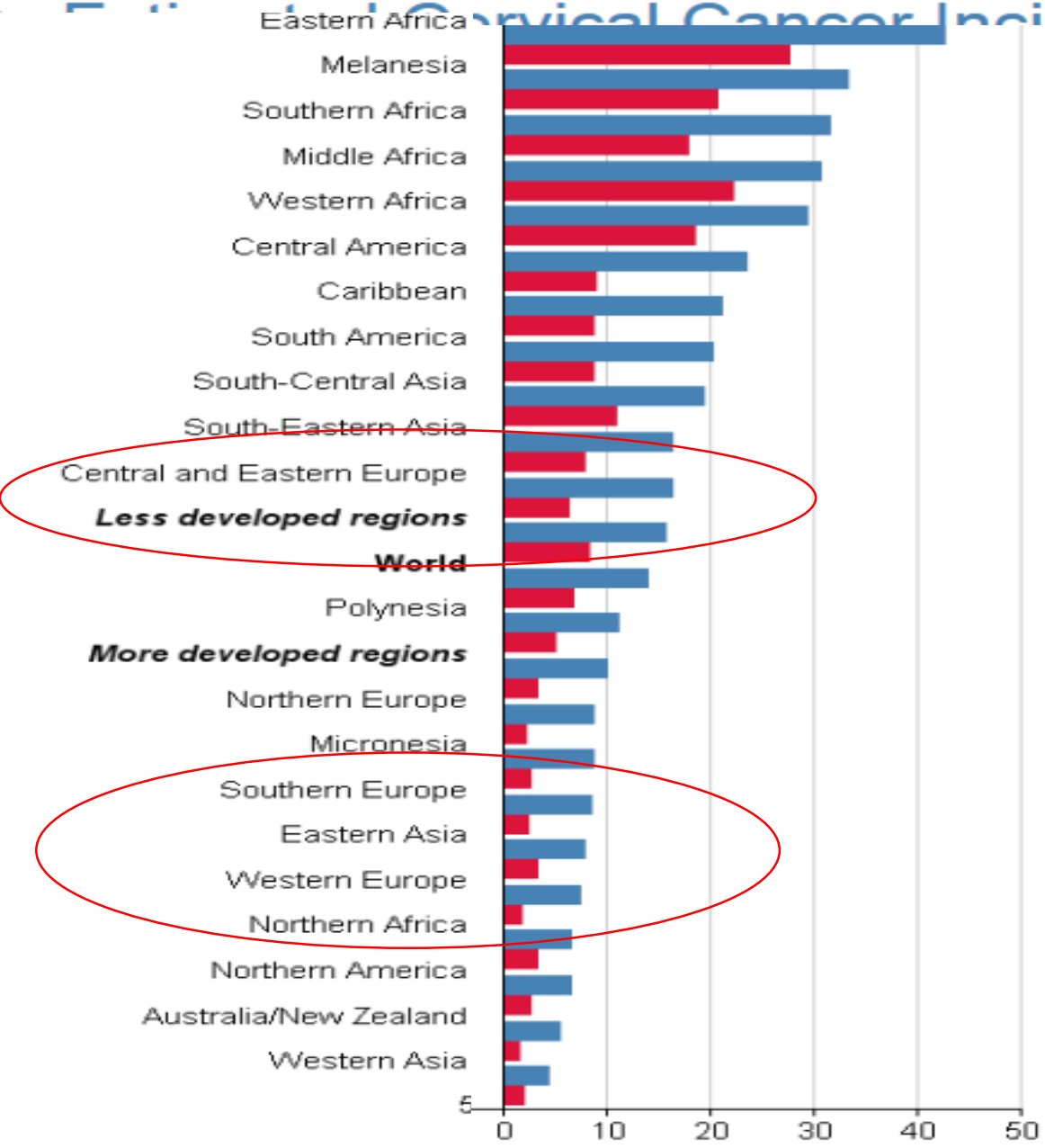
30% of all HPV-related cancers occur in men

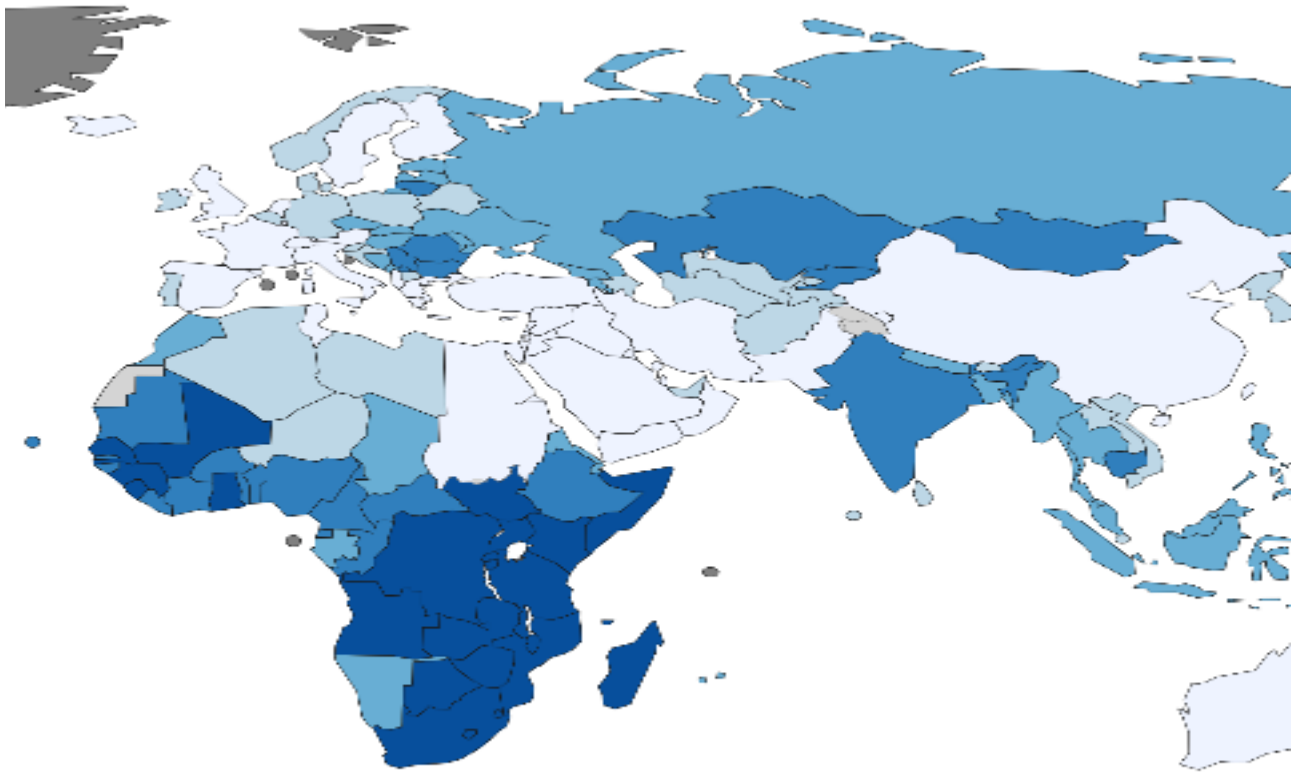




Schiffman, M. et al. N Engl J Med 2005;353:2101-2104

Estimated Cervical Cancer Incidence Worldwide in 2012





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The burden of HPV infections and induced lesions in HIV-positive patients

CD4 cell count decreases
HIV Viral load increases

- **HPV Infection**
  - Prevalence and incidence of HPV infection are higher.
  - **HPV viral load are higher. More infections with multiple genotypes.**
  - Clearance is decreased and recurrence of latent infection are frequent.
  - Persistent infection is significantly higher.
- **Precancerous lesions**
  - Prevalence and incidence of precancerous lesions are higher.
  - Spontaneous regression are less frequent.
  - Recurrence after treatment are more frequent.
- **Cancer**
  - Incidence 6-10 times higher for the cervix
  - Incidence 40 times higher for the anus

Slide courtesy
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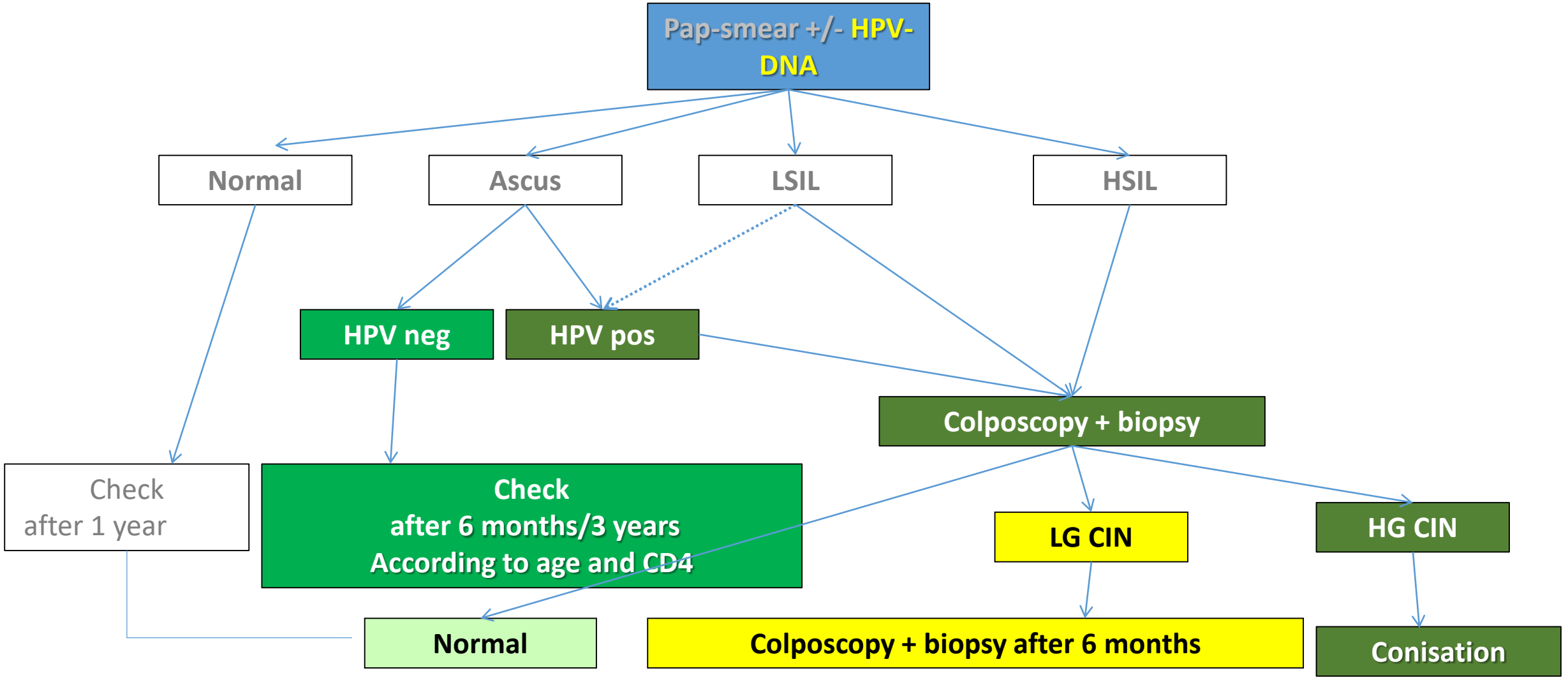
Preventive and therapeutic strategies to reduce HPV infection and induced lesions in HIV-positive women

Cervical screening

Slide courtesy
Deborah Konopnicki



Screening for cervical cancer

- Refer for screening at the first consultation
- If ≥30 years
    - Test for HRHPV
        - If HPV positive: colposcopy/biopsy
        - If HPV negative : next screen can be after
            - 3-5 years if CD4 high (>500/µL) and under cART
            - 1 year in other cases
- If <30 years
    - Cytology and colposcopy/biopsy

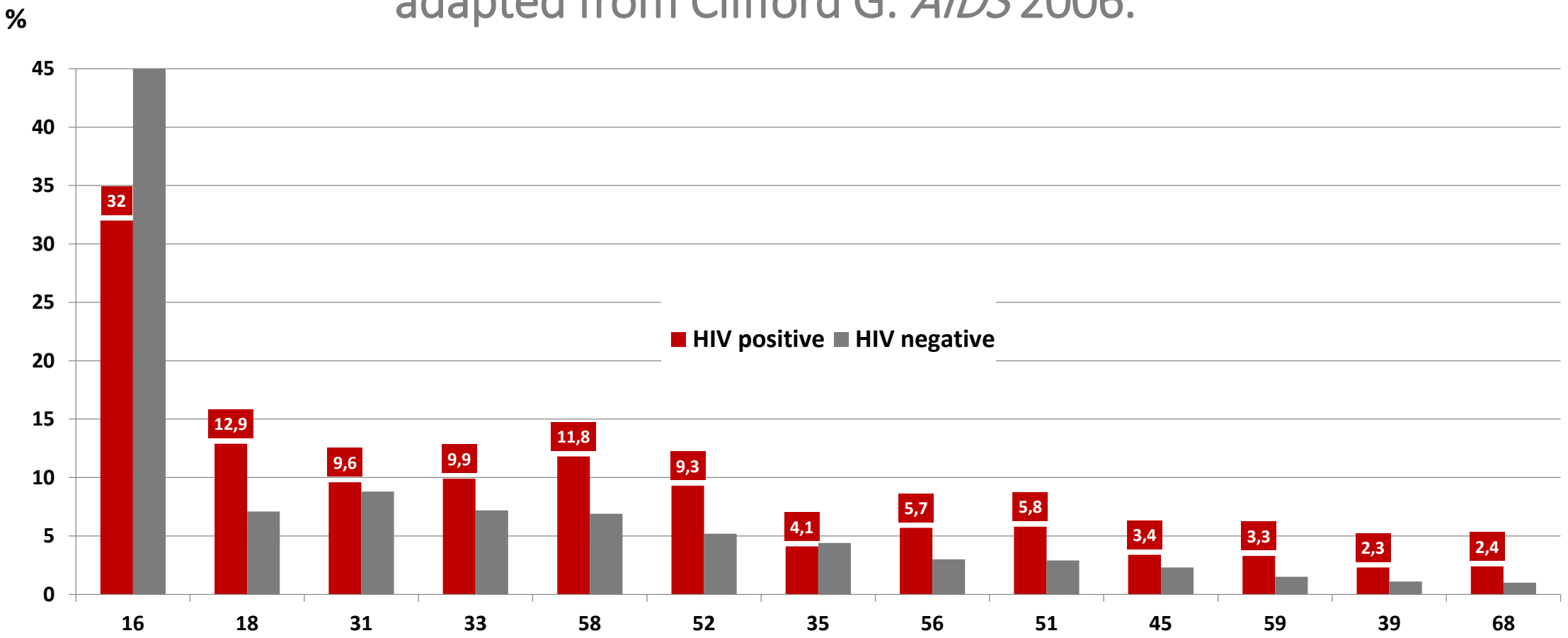
Slide courtesy
Deborah Konopnicki

Vaccinations available

	Bivalent (BHPV)	Quadrivalent (QHPV)	Nanovalent (NHPV)
	Cervarix®GSK	**Gardasil**®Merck	**Gardasil9**®Merck
HPV Genotypes	16/18	16/18 + 6/11	16/18/31/33/45/52/58 + 6/11
Adjuvant	ASO4 monophosphoryl lipid A = detoxified derivative of LPS of Salmonella adsorbed on aluminium	Aluminium	Aluminium
FDA/EMA approval	2007	2006	2014/15
	Females and males	Females and males	Females and males
	▪Precancerous lesions and cancer in the cervix, vulva or vagina and anus	▪Precancerous lesions and cancer in the cervix, vulva or vagina and anus ▪Genital warts	▪Precancerous lesions and cancer in the cervix, vulva or vagina and anus ▪Genital warts

HPV genotype distribution in HG CIN in HIV positive and negative women

adapted from Clifford G. *AIDS* 2006.



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Proportion of women infected with HRHPV genotypes that are included in the different vaccines

Prevalence of women of whom all or a part of HRHPV types are covered by	Current HPV vaccines including HRHPV 16 /18	Ninevalent HPV vaccine including HRHPV 16/18/31/33/45/52/58
Among all women (n=116)	24%	79%
Among women with abnormal cytology (n=44)	27%	82%

Konopnicki D and al.
AIDS 2015

Is vaccination indicated in patients with high grade lesions as secondary prophylaxis?

Women (HIV-negative)

- 2 randomised studies: Joura E. *BMJ* 2012.Woo Dae Kang. *Gynecol Oncol* 2013
- Decreased in recurrent lesions
  - **-65%** 2 years after treatment of CIN2-3 and vaccination
  - **-35%** 2 years after treatment of condyloma and vaccination

2.5% had recurrent CIN 2-3 among women vaccinated
vs 7.2% in non vaccinated women

How does it work?

- Strong HPV specific cell mediated immune responses in HIV-infected adolescents and young adults similar to HIV-negative
- 46 young adolescents/adults followed up to 28 weeks

Rainone V and al. AIDS 2015

HPV vaccination in people living with HIV

- Studies show good immunogenicity and response
- Good safety
- No adverse effects on CD 4 levels or viral load
- Induction of cellular immune response

Lavin Aids 2010
Wulkin JID 2010
Kojic CID 2014
Torfs CID 2014

Summary

- HPV-associated infections and lesions are **more frequent** and their outcome is **more severe** in persons living with HIV.
- **Preventive vaccines** against HPV are **safe and efficacious** and should be proposed to persons living with HIV as primary and secondary prevention strategies.
- **Antiretroviral therapy against HIV decreases HPV-associated infection and lesions** after several years of optimal viral control and immuno-restoration of high magnitude.
- Implementation or improvement of **HPV-related cancers screening** should be part of the HIV management.

Thank you very much for your attention

mail@aebi-popp.com

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