AV2® a key to cervical dysplasia regression?

JP Van geertruyden
HPV cancers = 90% cervical

HPV related cancer in women
527,100 cases WW/year

HPV related cancer in men
33,800 cases WW/year

90% of HPV cancer in women are cervical cancers

Adapted from Parkin DM, Bray F. Vaccine. 2006;24 Suppl 3:S11-25
Incidence distribution

- Heterogeneity in the world ~ prevention
- Estimated age-standardized incidence rates (2012 GLOBOCAN)

Sub-Saharan Africa has very high incidence rates in females >40 years old.

: 4. Age-specific incidence rates of cervical cancer in the sub-Saharan Africa region, and less or more developed regions. Data source: GLOBOCAN.
Cervical carcinogenesis

- 80% lifetime incidence
- HPV infection
- Normal cervix
- HPV-infected cervix
- Clearance
- HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82
- 2 to 15 years
- Regression
- Persistence 10-20%
- Severe dysplasia
- CIN1, LSIL, HSIL
- 10+ years
- Invasion
- Cancer

- Slow evolution
- Well defined non-invasive stages
- Histologically: CIN1, (CIN2), CIN3
- Cytologically: ASCUS, LSIL, HSIL

SCREENING
HPV dynamics function as a tier fountain

>Regression!
>non-evolution
### Interventions

1. **Prevention in the age-classes not yet at risk**

2. **Introduction of an effective and affordable HPV-vaccine in pre-sexual activity cohort**

3. **Minimize transmission and risk factors for progression**

4. **Pre-symptomatic Screening in risk groups**

5. **Treatment:**
   - Cryotherapy
   - Surgery
   - Radiotherapy
   - Palliative
AV2 related Regression

HPV infection

Normal cervix

HPV-infected cervix

Clearance

Persistence 10-20%

Regression

Severe dysplasia

Mild dysplasia

CIN1

LSIL

CIN3

HSIL
• **A broad spectrum virucide** (De-activation)
  - e.g. Parvo, HSV Clinical Trials

• **Prevents viral uptake at cell surface**
  - LPL Inhibitor

• **Both topical as oral treatment**
  - Cervical Lesions
  - Vaginal, penile and anal papilloma warts

• **Results in**
  - **Rapid clearing of the lesions**
  - **Slow shrinking of the warts**
    • Safe removal as virus is deactivated
• Observational case studies of a one-time spray of cutaneous skin warts (non-genital) did not show similar de-activation results.

• This is possibly due to the inhibiting factor of the cornified epidermis by denying access to the lipid bilayer as daily multiple sprays did show an effect after several weeks.
• **Oral** administering of AV2 for the treatment **Cervical HPV infections** showed no response.

• This is thought to be caused by the protective barrier of the cervix from the blood stream.
- **One time Spray** of AV2 directly on the cervical lesions

→ **Rapid regression** of the lesions indicating the de-activation of the virions.

→ **Possibly Stops Exit New Virions**
  - Still measure viral *particles* from basal cells without formation of new lesions
  - Electron microscopy study should bring clarity regarding LPL (Spring 2015)
Thus, medical treatment of cervical dysplasia with AV2® could offer a minimally invasive treatment with minor morbidity and time constraints.
Side effects AV2®

- **Orally**
  - no side effects have been observed.

- **Topically**
  - a warming/burning feeling similar to disinfecting alcohol on very sensitive areas such as the Labia minora and this for about 30-60 seconds.

For the patient's comfort, it is therefore advised to ask her to remain laying down for 3-4 minutes after application to the cervix.
Objective

• To evaluate the clinical efficacy of local AV2® virucide in the treatment of HPV-associated cervical lesions
  - To determine the genotypes of HPV found in the Kinshasa region.

• To test the impact of HPV screening followed by virucide treatment in a see-and-treat setting on HPV infection and associated cervical lesions.
  - to model the cost-effectiveness of:
    • VIA screening test and virucide treatment algorithm
    • VIA screening test and cryotherapy treatment algorithm
Inclusion criteria

- Sexually-active women;
- Women with intact uterine cervix;
- Voluntary written informed consent to participate in the study;
Exclusion Criteria

- Virgin women
- Pregnant, breast-feeding women, women in the post-partum
- Already diagnosed with cervical cancer.
- Medical history of any severe diseases like hepatitis, renal or liver dysfunction, cardiovascular, gastrointestinal, malignant tumor, or psychiatric disorders etc., which might influence the assessments or conduct of the trial by the discretion of the investigator.
- Intake or application of antivirals or other prohibited concomitant medication within 30 days prior to application of AV2®, or patients who plan to take such drugs during the trial.
- Known or suspected allergic or adverse response to the investigational product AV2® or its components (olive oil or d-limonene).
- Inability to follow the study protocol.
Study Flow Chart

VIA

No lesion: out of study, will be recalled for disclosure of HPV and LBC results

qPCR/LBC*

lesion

Randomize ACTIVE/placebo spray

After 2 months VIA

qPCR/LBC*

No lesion

lesion

cryotherapy

6 months after 1st visit: VIA

qPCR/LBC*

6 months after 1st visit: VIA

qPCR/LBC*

cancer: out of study, will be oriented for treatment as per local protocol

* qPCR and LBC for later analysis not available at randomisation or treatment
Outcomes

• **Primary outcome**  
  - Regression of lesions 2 months after treatment with AV2

• **Secondary outcomes**  
  - Absence of HPV DNA at month 2  
  - Changes in HPV viral particle load at month 6  
  - Number of participants with adverse effects
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Mexican trial

Randomized, double-blind, placebo-controlled trial comparing the clinical efficacy of AV2 and placebo over a 60-days period

>50% reduction
• for 21/28 (75%) patients in AV2® group versus
• 0% reduction in comparable placebo group.

Failed to respond positively
• 2 % of participants AV2® group versus
• 80% in the placebo group.
Herpes Labialis

• Short term results
  - New outbreak after the second irradiation
    • 9/11 Placebo group
    • 1/10 in the AV2 group
  - New outbreak vs active comparator
    • AV2: 15/19 (84%) had no outbreak.
    • Acyclovir (800): 7/17 (41%)
Herpes Labialis

- Long term results (2 years)
  - AV2 prevented 314/349 (90%) expected outbreaks
    - Intensity 35 outbreaks,
      - 10 = outbreaks are same in intensity as historical outbreaks.
      - 1 +
      - 24- (69%)
    - Regression vs expected outbreaks
      - 33/35 (94%) shorter as expected
Canine Parvovirus infection

- Oral administration (500 mg) 2 per day/ 7 days to 116 infected puppies.
- Result 6 puppies had died, a reduction in the predicted death rate of 80% to 5% ($p<0.0001$).
AV2® Composition

1a. D-carvone 2.5%
1b. L-carvone 2.5%
2. Eugenol 2.5%
3. Trans-Geraniol 2.5%
4. Cis/Trans?Nerolidol 5.0%
5. D-Glucose 15.0%
6. Olive Oil 70.0%