ANRS 1212 Study

Impact of HSV-2 episodic therapy on HIV-1 and HSV-2 genital shedding, and ulcer healing among women in Ghana and Central African Republic: randomised controlled trial

Philippe MAYAUD (LSHTM)
Background

• HIV transmission is enhanced in the presence of genital ulcer disease (GUD) \((\text{Gray, Lancet 2001})\)
• Increasing % of GUD due to HSV-2 in HIV+

Research questions

• Is HSV-2 really a cofactor of HIV transmission?
• Can HSV-2 be controlled? Will this have an impact on HIV transmission?
• By which method?
  – Prevention of GUD (role of suppressive therapy)
  – Treatment of GUD (role of episodic therapy)
  – Other (education, condoms, microbicides, vaccine?)
ANRS 1212 Trial

Multicentre, randomised, double-blind placebo-controlled trial of antiherpetic episodic treatment (acyclovir 400 mg x 3/d for 5 days) in addition to syndromic management (Ciprofloxacin + Benzathine penicillin 2.4 MU) among women with GUD in Ghana and Central African Republic

Exclusion criteria:
- indications for immediate ACV (large or chronic ulcers)
- contra-indications of ACV (pregnant, breast-feeding, renal failure, history of “allergy” to ACV)
ANRS1212: Study Outcomes

(Primary analysis group: HIV-1 +ve women with HSV-2 ulcers)

Outcomes:

1) Detection, frequency, and quantity of cervico-vaginal (CV) HIV-1 RNA* among HIV-1/HSV-2 co-infected women

2) Detection of lesional HIV-1 RNA*
   Quantity of plasma HIV-1 RNA*
   Detection, frequency and quantity of cervico-vaginal (CV) HSV-2 DNA*

3) Ulcer aetiologies (PCR) and healing rates (size)

* using real-time PCR; Methods in Legoff J et al, J Clin Microbiol 2006;44: 423-32
## Enrollment by site: Total trial population

<table>
<thead>
<tr>
<th>Site</th>
<th>Synd+Placebo n (%)</th>
<th>Synd+ACV n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCRA (n=121)</td>
<td>60 (27%)</td>
<td>61 (28%)</td>
</tr>
<tr>
<td>KUMASI (n=163)</td>
<td>82 (37%)</td>
<td>81 (37%)</td>
</tr>
<tr>
<td>BANGUI (n=157)</td>
<td>78 (35%)</td>
<td>70 (36%)</td>
</tr>
<tr>
<td>Total (n=441)</td>
<td>220</td>
<td>221</td>
</tr>
</tbody>
</table>
Baseline data

HSV-2 ulcers 50% (only 3% have bacterial etiol.)
HSV-2 sero+ 79%
HIV-1 sero+ 47%
Dually sero+ 41% (n=179)

Plasma HIV-1 RNA
5.13 vs. 4.64 log_{10} c/mL (P=0.03)
### Enrolment, follow-up, compliance

- **490 women presented**
- **449 eligible**
- **441 randomized**

**220 Placebo arm**
- **64 HIV+ with HSV2 ulcer**
- **48 analysed on day 7 (75%)**

**221 ACV arm**
- **54 HIV+ with HSV2 ulcer**
- **42 analysed on day 7 (78%)**

**Mean compliance rate (pill count) = 99% in both arms**

**Side effects:** 8/441 (2%, severity 1 or 2)

**Primary analysis group:**
- **118 HIV+ women with HSV-2 ulcer**
## Participants characteristics in primary analysis

**group (HIV+ women with HSV-2 ulcers) (N=118)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SM+Placebo (n=64)</th>
<th>SM+ACV (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years</td>
<td>31.4</td>
<td>30.8</td>
</tr>
<tr>
<td>Median CD4 count (/µL) (IQR)</td>
<td>188 (72-519)</td>
<td>194 (92-548)</td>
</tr>
<tr>
<td>Taking HAART</td>
<td>5 (8%)</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Experienced GUD last year</td>
<td>27 (42%)</td>
<td>25 (47%)</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>3 (5%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Trichomonas vaginalis</em></td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Serological syphilis</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Impact of ACV on frequency of CV HIV-1 RNA detection at day 7 among HIV+ women with HSV-2 ulcers (N=90)

\[
\text{RR*} = 0.93 \\
(0.8 - 1.1)
\]

* Adjusted for site and baseline CV HIV-1 RNA
Impact of ACV on frequency of lesional HIV-1 RNA detection at day 7 among HIV+ women with HSV-2 ulcers (N=76)

RR* = 0.75 (0.3 – 1.2)

* Adjusted for site
Impact of ACV on HIV-1 viral loads

- Little impact on mean cervico-vaginal HIV-1 RNA at day 7 (-0.11 log_{10} copies/mL, \( P=0.53 \))

- No impact on mean plasma HIV-1 RNA at day 14 (0.04 log_{10} copies/mL, \( P=0.76 \))
Impact of ACV on HSV-2 at day 7

- Reduction from:
  - 81% at D0 to 26% at day 7 in acyclovir arm,
  - 81% at D0 to 35% at day 7 in placebo arm

=> RR=0.73 (P=0.2)

- Mean quantity HSV-2 DNA was $1.2 \log_{10}$ copies/mL lower in acyclovir arm than placebo arm (P=0.004)
Proportion of women with CV HSV-2 DNA over time in HIV+ women with HSV-2 ulcers.

%HSV2 genital shedding

- Placebo arm
- Acyclovir arm
Mean HIV-1 and HSV-2 viral loads over time

Viral load over time by arm

Placebo arm

Acyclovir arm

Mean HIV and HSV viral loads over time.
Impact on ulcer healing at day 7 in HIV+ women with HSV-2 ulcers

<table>
<thead>
<tr>
<th></th>
<th>D0</th>
<th>D7</th>
<th>Magnitude</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plac.</td>
<td>Plac. ACV</td>
<td>Plac. ACV</td>
<td>RR=1.23</td>
<td>0.06</td>
</tr>
<tr>
<td>% ulcers with &gt;90% size reduction</td>
<td>44%</td>
<td>55%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% with ulcers &lt;10 mm²</td>
<td>10%</td>
<td>0%</td>
<td>42%</td>
<td>58%</td>
</tr>
<tr>
<td></td>
<td>RR=1.48</td>
<td></td>
<td></td>
<td>0.02</td>
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Ulcer healing rates over time: HIV+ women with HSV-2 ulcers

Some impact of ACV among HIV+ women with HSV-2 ulcers ($P=0.10$)

No impact overall on ALL HIV+ women

Ulcers healed faster in women with higher CD4 count ($P=0.0002$)
Episodic ACV has no measurable (immediate) impact on HIV-1 genital shedding:
- Late treatment (median 7 days after ulcer first noticed by woman)
- Insufficient duration of treatment (5 days)?
- Insufficient dose of standard regimen?
- Delayed effect on genital HIV load (day 28 or later)?
- Advanced HIV disease in many women
- Lack statistical power?

ACV does:
- Decrease frequency and quantity of CV HSV-2 DNA
- Improve healing rates, particularly among HIV+ with low CD4

HSV-2 the dominant GUD aetiology:
- Associated with high HIV-1 sero-prevalence
- Associated with high HIV-1 viral loads (similar to levels observed in HIV-1 primary infection for PVL)
Programmatic implications

(1) Syndromic Management of GUD
   – Need to remove antibiotics? **No** (*healing, HIV shedding*)
   – Need to add ACV? **Yes** (*cautiously… clin + epi impact?*)

(2) Offering HIV testing to patients with GUD (+++)
   – for **HIV positive patients**:
     • Access ARV+++ 
     • Explain frequent HSV reactivation 
     • Possibly offer suppressive treatment
   – for **HIV negative patients**:
     • Explain risk of HIV acquisition, reinforce prevention messages 
     • HSV disease education and benefits of **early** Rx
Research implications

- For prevention of **HIV transmission**:
  - Await results of other trials in Malawi & South Africa

- For prevention of **HIV acquisition**:
  - High risk of HIV seroconversion (particularly PGH)
  - Should be better studied

- Relative roles of **episodic** vs. **suppressive** treatment, or **combination for HIV+ patients**?
  - Longer duration of episodic treatment?
  - Initiation of suppressive treatment
  - Operational research/trials required
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