Efficacy of HSV-2 suppressive therapy on HIV-1 shedding and plasma viral load among co-infected women receiving or not HAART in Burkina Faso (ANRS 1285 trials)

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Influence of genital ulcerations

HIV-1 transmission probability per sexual intercourse in sero-discordant couples in Rakai, Uganda

(Gray RH et al., Lancet 2001)

Plasma HIV-1 load in infected partner (copies/ml)
Proportion of genital herpes or HSV-2 isolation (culture/PCR) over time among GUD patients in sub-Saharan Africa settings.

Median Plasma HIV RNA Before, During, and After Acyclovir Suppression among 12 MSM in Seattle

(Schacker et al. JID 2002)
Herpes Simplex Virus Infection Induces Replication of HIV-1

Co-infection of the same keratinocyte by HSV-1 and HSV-2 virions. Non-enveloped HSV-1 (N) in A and enveloped HSV-1 (2) in B. Atypical HIV in envelope (1), core (2) and membranes (3); typical HIV in B.

Heng et al. Lancet 1994
Design

Proof of concept double blind randomized controlled trials of daily valacyclovir 1000mg vs. placebo among co-infected women not eligible for HAART or taking HAART

**Study endpoints:**

1/ Detection and pattern of HIV-1 shedding and mean quantity of genital HIV-1 RNA

2/ - Mean quantity of plasma HIV-1 RNA
   - Detection and pattern of HSV-2 shedding and mean quantity of genital HSV-2 DNA
   - Occurrence of genital ulceration or vesicles
**Baseline Phase**

- FSW cohort (n=650)
- Screening 1: HIV, HSV2, pregnancy
- Screening 2: CD4+ count, creatinin

**Treatment Phase**

- ANRS 1285a (n=150)
- P or V*
- ANRS 1285b (n=60)
- HAART

* Placebo or Valacyclovir 1000mg daily, first dose given the same day just after genital sampling
Laboratory procedures

• **Genital sample:** enriched cervico-vaginal lavage

• **HSV-2 serology**
  – Kalon test: best performance (98% specificity and 95% sensitivity, Van Dyck et al., JCM 2004)

• **Outcome measurements**
  – Real Time PCR (ABI 7000)
    • HSV-2 DNA (threshold=500 copies/mL)
    • Genital HIV-1 RNA (threshold=300 copies/mL)
    • Plasma HIV-1 RNA (threshold=350 copies/mL)
    • Technology transfer to BF, QC scheme
  – CD4 count by Facscount
  – CT by PCR & NG by culture
1285a: enrolment, follow-up, compliance

195 women screened

\[\downarrow\]

150 enrolled (baseline)

\[\downarrow\]

140 randomized

\[\downarrow\]

70 Placebo arm

[68 analysed (2 HIV-2 positives)]

[6 censored]

70 VACV arm

[68 analysed (2 HIV-2 positives)]

[5 censored]

93% visits attended

Mean compliance rate (pill count) = 97% in both arms
82 women screened

61 enrolled (baseline)

60 randomized

30 Placebo arm

30 analysed

0 censored

30 VACV arm

30 analysed

2 censored

97% visits attended

Mean compliance rate (pill count) = 99%

Median HAART duration: 19.3 wks (IQR 18-25) (90% compliance)
### Baseline participants characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Valacyclovir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age in years (SE)</strong></td>
<td>32.5 (0.89)</td>
<td>31.5 (0.93)</td>
</tr>
<tr>
<td><strong>Median CD4 count (/µL) (IQR)</strong></td>
<td>433 (316-621)</td>
<td>447 (328-655)</td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em></td>
<td>2 (2.9%)</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td><em>Trichomonas vaginalis</em></td>
<td>4 (5.6%)</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Serological syphilis</td>
<td>0</td>
<td>1 (1.4%)</td>
</tr>
</tbody>
</table>
ANRS 1285a
Proportion of women with HIV-1 genital shedding per visit per arm
## Impact of VACV on detection of genital HIV-1 RNA

<table>
<thead>
<tr>
<th></th>
<th>ANRS 1285a (n=136)</th>
<th>ANRS 1285b (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% visits with HIV-1 genital shedding</strong></td>
<td>OR=0.47, 95%CI: 0.28-0.78 (p=0.003)</td>
<td>OR=1.00, 95%CI: 0.39-2.56 (p=1.00)</td>
</tr>
<tr>
<td></td>
<td><strong>Among HIV-1 base shedders:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR=0.27, 95%CI: 0.07-0.99 (p=0.048)</td>
<td></td>
</tr>
<tr>
<td><strong>Frequency/pattern of genital shedding (per woman analysis)</strong></td>
<td>OR=0.41, 95%CI: 0.21-0.80 (p=0.009)</td>
<td>OR=0.90, 95%CI: 0.31-2.62 (p=0.85)</td>
</tr>
</tbody>
</table>
## Impact of VACV on quantity of genital & plasma HIV-1 RNA

<table>
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<th>ANRS 1285a (n=136)</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Quantity of genital HIV-1 RNA</strong></td>
<td>- 0.41 log_{10} #&lt;br&gt;95%CI: -0.21, -0.80&lt;br&gt;(p=0.009)</td>
<td>- 0.33 log_{10} *&lt;br&gt;95%CI: -0.80, 0.16&lt;br&gt;(p=0.19)</td>
</tr>
<tr>
<td><strong>Among HIV-1 baseline shedders</strong></td>
<td>-0.71 log_{10} *&lt;br&gt;95%CI: -1.27, -0.14&lt;br&gt;(p=0.013)</td>
<td></td>
</tr>
<tr>
<td><strong>Quantity of plasma HIV-1 RNA</strong></td>
<td>- 0.58 log_{10} #&lt;br&gt;95%CI: -0.79, -0.37&lt;br&gt;(p&lt;0.001)</td>
<td>- 0.41 log_{10} *&lt;br&gt;95%CI: -1.35, 0.53&lt;br&gt;(p=0.39)</td>
</tr>
</tbody>
</table>

# *Per woman* analysis (compares mean HIV-1 RNA per arm and phase)<br>
* *Per visit analysis*, among all *visits* with detectable HIV-1 RNA
### Impact of VACV on detection of genital HSV-2 DNA and GUD occurrence

<table>
<thead>
<tr>
<th></th>
<th>ANRS 1285a (n=136)</th>
<th>ANRS 1285b (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% visits with detectable HSV-2 DNA</td>
<td>OR=0.24 95%CI: 0.11, 0.51 (p&lt;0.001)</td>
<td>OR=0.37 95%CI: 0.13, 1.05 (p=0.06)</td>
</tr>
<tr>
<td>Mean genital HSV-2 DNA (visits)</td>
<td>- 0.14 log(_{10}) * (p=0.77)</td>
<td>- 1.18 log(_{10}) * (p=0.12)</td>
</tr>
<tr>
<td>GUD occurrence</td>
<td>RR=0.16 (p=0.002)</td>
<td>-</td>
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</tbody>
</table>

* Per visit analysis, among all visits with detectable HIV-1 RNA
<table>
<thead>
<tr>
<th></th>
<th>Baseline phase</th>
<th>Treatment phase</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>VACV</td>
<td>Placebo</td>
</tr>
<tr>
<td>GUD ≥ 1</td>
<td>27.9%</td>
<td>29.4%</td>
<td>27.9%</td>
</tr>
<tr>
<td>HSV-2 shedders</td>
<td>45.6%</td>
<td>44.1%</td>
<td>54.4%</td>
</tr>
<tr>
<td>HSV-2 detected:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No visit</td>
<td>54.4%</td>
<td>55.9%</td>
<td>45.6%</td>
</tr>
<tr>
<td>1-49% visits</td>
<td>38.2%</td>
<td>46.2%</td>
<td>41.3%</td>
</tr>
<tr>
<td>50-99% visits</td>
<td>7.3%</td>
<td>1.5%</td>
<td>11.7%</td>
</tr>
<tr>
<td>All visits</td>
<td>0</td>
<td>0</td>
<td>1.5%</td>
</tr>
<tr>
<td>Mean genital HSV-2 DNA</td>
<td>4.56 (n=50)</td>
<td>4.82 (n=38)</td>
<td>4.63 (n=68)</td>
</tr>
</tbody>
</table>
## Summary Results

<table>
<thead>
<tr>
<th></th>
<th>1285a (N=136)</th>
<th>1285b (N=60)</th>
<th>1285b (b shedders) (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genital HIV-1 RNA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td></td>
<td>←→</td>
<td>←→</td>
</tr>
<tr>
<td>Quantity ((\log_{10} \text{ copies/mL}))</td>
<td>- 0.41</td>
<td>←→</td>
<td>←→ - 0.71</td>
</tr>
<tr>
<td><strong>Plasma HIV-1 RNA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td></td>
<td>←→</td>
<td>←→</td>
</tr>
<tr>
<td>Quantity ((\log_{10} \text{ copies/mL}))</td>
<td>- 0.58</td>
<td>←→</td>
<td>←→ - 0.41</td>
</tr>
</tbody>
</table>

Rx effect increased over time: \(-0.11 \log_{10}\) (CI: 0.06, 0.16) every 2 weeks for genital HIV-1 and \(-0.10 \log_{10}\) (CI: 0.06, 0.14) for plasma HIV-1 RNA (p<0.001)
Discussion (1)

• Causal link between HSV-2 and HIV-1 replication
  – Proven, likely to persist while on HAART
  – Potential mechanisms for the impact of VACV on HIV-1:
    • Indirect role since ACV has no pharmacological effect on HIV-1
    • Biological explanations
    • Through impact on other latent Herpesviridae?
Discussion (2)

- **Genital compartmentalisation of HIV-1 replication**
  - 2/3 women with fully active HAART can potentially transmit HIV-1
    - Longitudinal data ++
    - Reinforce safe sex promotion among these patients
  - Poor genital penetration of d4T and EFV (Dumont et al., CROI 2006): selection of mutations?
  - VACV impacted on the genital independent HIV replication (may explain residual shedding of women on HAART)
Probable mechanisms involved

HIV viral load

HAART

“systemic” HIV shedding

“local” HIV shedding

HSV shedding

HIV transmission

Systemic compartment

ANTIHERPETIC SUPP. THERAPY

Genital compartment

HIV transmission
HSV suppressive therapy

- Safe, no lab monitoring required
- HSV resistance is rare, even among HIV infected individuals (<5%)

**Potential benefits on HSV-2 infection:**
- Prevention of clinical episodes
- Marked reduction in HSV-2 shedding: impact on HSV-2 transmission?
- More data required for effect of ACV with HAART

- Additional impact on other Herpes simplex viruses?
Potential benefits on HIV-1 infection

• **HIV-1 transmission:**
  - Impact on genital HIV-1 RNA = decreased transmission?

• **HIV-1 disease:**
  - Need for clinical outcomes: does impact on PVL leads to slower CD4 decline?
  - Confirmation from other settings
  - Role during HAART?

• **HIV acquisition:** ongoing effectiveness trials. Initiation during primary genital herpes?
Ongoing HSV suppressive Rx trials

HIV-1 acquisition:
- HPTN039 (University of Washington), men & women
- Mwanza (LSHTM), sex workers (ends summer 07)

HIV-1 transmission:
- Large multicentre suppressive RCT among serodisc. couples (n>3000), (Univ. of Washington)

HIV shedding & HIV plasma viral load
- South Africa: 300 women, 3 months follow-up
- Tanzania: 400 FSW, 12 months follow-up
- Peru: 20 MSM
- ‘Partners in Prevention’ trial
Future research…

• Extrapolation of these results to men?
• Impact of VACV on the long run before HAART, with immunological outcomes: individual benefits?
• Quantify the reduction in HIV-1 transmission
• Benefit of ACV on patients taking HAART (fully active or not)
• Cost-effectiveness and acceptability studies
• New vaccine concepts (both prophylactic and therapeutic) and develop the promising ones

Boost HSV vaccine research
Acknowledgements

- Local NGOs of PLWHAs
- Infectious Disease ward personnel (Bobo-Dioulasso Hospital)
- Regional Health Director and his team
- ANRS for their support

AND MANY THANKS TO ALL PARTICIPANTS