Herpes simplex virus type-2 (HSV-2) suppressive therapy to reduce genital and plasma HIV-1 RNA: overview of ANRS1285 trials, potential mechanisms and future interventions

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HSV-2 – HIV-1: Double Trouble

• HSV-2 facilitates HIV-1 acquisition (*Freeman E et al. AIDS 2006*)

• >80% of HIV-1 infected individuals are co-infected with HSV-2 in Africa

• HIV alters the natural history of HSV-2

• HSV-2 may potentially increase HIV-1 transmissibility through increased shedding

=> RCTs required to demonstrate a causal role of HSV-2 on HIV-1 replication and transmissibility, at all stages of HIV disease, incl. HAART
Design & Study Outcomes

Proof-of-concept double-blind randomized trials of daily valacyclovir 500mg BD for 3mo. vs. Placebo among dually HIV-1 / HSV-2 sero+ women, either not eligible for HAART (ANRS 1285a), or taking HAART for >4 mo. (ANRS 1285b)

Study Outcomes:

1. Detection, frequency & quantity of cervico-vaginal (CV) HIV-1 RNA

2. Quantity of plasma HIV-1 RNA
   Detection, frequency & quantity of CV HSV-2 DNA
   Occurrence of genital ulcerations

3. Compliance and side effects rates
Laboratory Methods

- Serologies: HIV-1, HSV-2 (Kalon® gG2), syphilis
- HIV plasma viral load (real time PCR) - monthly
- CD4 cell count by FACSCAN – once/phase
- Standardised enriched cervico-vaginal lavage (eCVL) (Nagot N et al, JAIDS 2005) - bi-weekly
- HIV-1 RNA and HSV-2 DNA quantitated by real-time PCR, using external standards for QC (ANRS HIV, HSV 1/2 Clear QC)
FSW cohort → Screening: HIV, HSV-2, Hx of recurrences, pregnancy, lactating, creatinine, CD4

ANRS 1285a → Baseline phase

ANRS 1285b → Treatment phase

HAART* → P or V

* First line: AZT or stavudine [d4T] + lamivudine [3TC] + efavirenz [EZV]
Statistical Methods

- Modified Intention to Treat approach (censoring incident pregnancy)

- Summary measure (per woman) analysis
  - Quantitative outcomes: linear regression
  - Qualitative outcomes: (ordered) logistic regression

- Repeated measures analysis (per visit) analysis
  - Random effects models

- Pre-specified subgroup analyses (1285b)
  - Women shedding HIV-1 at least once over the baseline phase
ANRS 1285a: Enrolment, follow-up, compliance

195 women screened

150 enrolled (baseline)

140 randomized

70 Placebo arm

70 VACV arm

68 analysed
(2 HIV-2 +ve excl.)

68 analysed
(2 HIV-2 +ve excl.)

6 censored

5 censored

93% visits attended

Mean compliance rate (pill count) = 97% in both arms
ANRS 1285b: Enrolment, follow-up, compliance

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)
HAART adherence >90%
ANRS 1285a (non-HAART)

Proportion of women with detectable genital HIV-1 RNA by visit, treatment arm and study phase
Summary Results: Impact on HIV-1

<table>
<thead>
<tr>
<th></th>
<th>1285a (N=136)</th>
<th>1285b (N=60)</th>
<th>1285b (base. shed.) (N=30)</th>
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<tbody>
<tr>
<td><strong>Genital HIV-1 RNA</strong></td>
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<tr>
<td>Frequency</td>
<td></td>
<td>←</td>
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<tr>
<td>Quantity (log₁₀ copies/mL)</td>
<td>-0.41</td>
<td>←</td>
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<td></td>
<td></td>
<td></td>
<td>← -0.71</td>
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<tr>
<td><strong>Plasma HIV-1 RNA</strong></td>
<td></td>
<td></td>
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<tr>
<td>Frequency</td>
<td>←</td>
<td>←</td>
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</tr>
<tr>
<td>Quantity (log₁₀ copies/mL)</td>
<td>-0.58</td>
<td>←</td>
<td>← -0.41</td>
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</table>

Effect increased over time: \(-0.11 \log₁₀\) (CI: 0.06, 0.16) every 2 weeks for genital HIV-1 and \(-0.10 \log₁₀\) (CI: 0.06, 0.14) every month for plasma HIV-1 RNA (p<0.001)
Impact of VACV on HSV-2 and ulcers

- Women not taking HAART (1285a):
  - Reduction of genital HSV-2 by 65% (54% to 19% of visits)
  - Reduction of occurrence of ulcers by 84% (30% to 4.4% of visits)

- Women on HAART (1285b):
  - Very little HSV-2 shedding, but further reduced by 70%
  - No ulcer occurrence in both arms
Discussion (1)

- **First RCT to demonstrate causal relationship between HSV-2 and HIV-1 replication**
  - Effect still persists while on HAART (1285b, baseline shedders).
  - Potential mechanisms:
    - no direct antiretroviral effect of VACV
    - known biological interactions (afflux of CD4+; HSV proteins transactivate HIV tat or LTR) – role of lesions?
    - impact on other Herpesviridae (HSV-1, CMV, EBV HHV-6)?

- **Impact on genital HIV-1 RNA and plasma HIV-1 RNA**
  - Sufficient impact to reduce HIV-1 transmission?
    - => Await results of ongoing trials among sero-discordant couples (C. Celum)
  - Could virological impact at systemic level be translated into impact on CD4?
    - ⇒ Specific trials needed? Operational research?
Discussion (2)

• Genital compartmentalisation of HIV-1 replication
  – Suggested by results of ANRS1285b
  – Two-thirds of women with fully active HAART shed HIV at some point and could potentially transmit HIV-1
    => safe sex promotion to be emphasized
  – Poor genital penetration of d4T and EFV (Dumont et al., CROI 2006)
    => selection (and transmission?) of HIV mutants?
Possible mechanisms of action

- HIV viral load
- Systemic compartment
- HAART
- SUPPRESSIVE THERAPY
- Genital compartment
- HIV transmission

Possible mechanisms of action:

- "Systemic" HIV shedding
- "Local" HIV shedding

Possible mechanisms of action:

- HSV shedding

HIV transmission

Possible mechanisms of action:

- Treatment options

Possible mechanisms of action:

- HAART

Possible mechanisms of action:

- Suppressive therapy

Possible mechanisms of action:

- Prevention strategies
HSV suppressive therapy: Important Remaining Questions

1) Is it safe and practical to use?
   - few side effects, no lab monitoring required, resistance is rare (<5% in HIV+), good compliance possible

2) What will be the potential benefits?
   - on HSV-2: clinical episodes, shedding, HSV transmission?
   - on other Herpesviridae? (co-morbidity)
   - on HIV transmission? disease progression? acquisition?

3) In which populations should it be offered?
   - High-risk groups?
   - Sero-discordant couples?
   - In HIV+: before HAART? during HAART?
HSV-2 potential control tools

- No HSV-2 infection
  - Prophylactic vaccine?
- Primary infection and shedding
  - Episodic treatment
- Latent infection
  - Suppressive therapy
  - Therapeutic vaccine?
- Clinical recurrences
  - Episodic treatment
- Sub-clinical recurrences
  - Episodic treatment
For More Information

• ANRS Symposium, Tues 15/08, 18:00, Skills Building Room #3

• ANRS 1285a: CROI Feb 2006 (Nagot N et al, Abs# 33LB)

• ANRS 1285b: Poster TuPE0402 (Nagot N et al) and AIDS 2006 (in press)