HPTN 039:
A phase III, randomized, double-blind, placebo-controlled trial of acyclovir for the reduction of HIV acquisition among high-risk HSV-2 seropositive, HIV seronegative persons

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Acknowledgments

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- Jim Hughes, Statistician
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  - Susan Buchbinder, Jon Fuchs, Beryl Koblin (US)
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- Central Laboratory: Estelle Piowar-Manning (Hopkins); Anne Cent, Rhoda Morrow, Meei-li Huang, & Bob Coombs (UW)
- DSMB, IRBs, CABs
- Sponsor: Division of AIDS, NIAID, NIH
- Study Participants
HSV-2 increases HIV susceptibility

- **Epidemiologic Data**
  - Longitudinal studies which adjusted for age & sexual behavior (n=18)
  - Prevalent HSV-2 infection and HIV acquisition
    - Men \text{RR} 2.7 \ 95\% \text{CI} 1.9-3.9
    - Women \text{RR} 3.1 \ 95\% \text{CI} 1.7-5.6
    - MSM \text{RR} 1.7 \ 95\% \text{CI} 1.2-2.4
  - 38-69\% of new HIV infections in ♀ & 8-49\% in ♂ due to prevalent HSV-2
    (Freeman AIDS 2006)

- **Biologic Plausibility**
  - HSV-2 causes macro- & microscopic ulcerations
  - HSV-2 reactivation is frequent: 20\% of days HSV PCR+ in HIV-negative persons
    (Mark ISSTDR 2007)
  - ↑ cervical CD4 T cells & immature dendritic cells in HSV-2 seropositive women
    (Rebbapragada AIDS 2007)
HPTN 039: HSV-2 suppressive therapy to prevent HIV acquisition

- HIV- HSV-2+ heterosexual women
  - Harare, Zimbabwe
  - Lusaka, Zambia
  - Johannesburg, South Africa

- HIV- HSV-2+ MSM
  - Lima, Iquitos, Pucallpa: Peru
  - Seattle, San Francisco, NYC

Randomize

- Acyclovir 400 mg bid
- Matching Placebo bid

Both arms received episodic ACV for GUD & risk reduction counseling

1° endpoint: HIV infection
Assumptions and Analyses

- Sample size assumptions:
  - 50% effect size
  - 90% power
  - 3.5% HIV incidence in placebo arm

- Primary analysis: Intent-to-treat

- Risk estimates adjust for gender, age, GUD at enrollment & # of sex partner in last 12 months at entry

- Additional analyses adjust for sexual behavior during the study as time-dependent covariates

- Adherence measured by monthly pill count & self report
Entry criteria

- Age of informed consent (≥18 yrs)

- HIV negative

- HSV-2 seropositive
  - Focus EIA index value > 3.4; confirmed with UW HSV Western blot

- Behavioral criteria
  - Women from southern Africa:
    - ≥1 episode of unprotected vaginal sex in past 6 months

  - MSM from U.S. and Peru:
    - ≥1 episode of anal intercourse in past 6 months & not mutually monogamous with HIV- man
Monthly visit procedures

- Ascertain adherence by pill count & self report
- Counsel about adherence
- Dispense study drug
- Questionnaire about GU history, STD symptoms and sexual behavior
- Genital exam & syndromic therapy (if symptomatic)
- Safer sex counseling & condom provision
Additional study procedures

- Quarterly visits
  - Blood draw for HIV antibody
  - Genital exam
  - Swabs for HSV if ulcers present

- Episodic acyclovir offered for genital herpes recurrences

- Pregnant women taken off study drug, given limited experience with ACV in pregnancy in Africa
  - Continued in study & drug restarted after pregnancy
Follow up

- Initially for 1 year
- Extended to 18 months, due to accrual rate
- Primary analysis included all appropriately enrolled participants
- To avoid potential bias, excluded data for 12-18 months from primary analyses from 2 sites that did not achieve >94% re-consent rate
Assessed for eligibility
(N=11731)

Reasons for exclusion (n=7546; categories not mutually exclusive)
- HIV positive (1571)
- HSV-2 negative or low positive (4322)
- other

3277 randomized

1537 intervention
8 HIV+ at enrollment 3 Duplicate enrollments

Follow-up at quarterly visits:
3 mo: 1498/1626 (92%)
6 mo: 1475/1626 (91%)
9 mo: 1442/1626 (89%)
12 mo: 1422/1626 (87%)
15 mo: 1027/1212 (85%)
18 mo: 1028/1212 (85%)

1640 control
13 HIV+ at enrollment 2 Duplicate enrollments

Follow-up at quarterly visits:
3 mo: 1513/1625 (93%)
6 mo: 1488/1625 (92%)
9 mo: 1469/1625 (90%)
12 mo: 1450/1625 (89%)
15 mo: 1027/1208 (85%)
18 mo: 1030/1208 (85%)

45 HSV2 negative at enrollment
1531 analyzed

34 HSV2 negative at enrollment
1591 analyzed
Study population

- Total enrolled: 3277
- Inappropriately enrolled: 105
  - HIV PCR+ at enrollment, duplicate enrollment, HSV-2 neg by Western blot
- Appropriately enrolled: 3172
  - MSM, Peru sites: 1355
  - MSM, U.S. sites: 459
  - Women, Africa sites: 1358
- Retention at 18 months: 85% in both arms
## Demographic & behavioral characteristics at enrollment

<table>
<thead>
<tr>
<th></th>
<th>Women N = 1358</th>
<th>Peru MSM N = 1355</th>
<th>U.S. MSM N = 459</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>31</td>
<td>28</td>
<td>40</td>
</tr>
<tr>
<td>&lt;secondary education</td>
<td>96%</td>
<td>61%</td>
<td>16%</td>
</tr>
<tr>
<td># SP, past year (median)</td>
<td>1</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td># SP, past month (median)</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td># sex acts past 3 months</td>
<td>24</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Any unprotected vaginal sex, past 3 months</td>
<td>90%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Any unprotected receptive anal sex, past 3 months</td>
<td>-</td>
<td>56%</td>
<td>33%</td>
</tr>
<tr>
<td>Any unprotected insertive anal sex, past 3 months</td>
<td>-</td>
<td>21%</td>
<td>40%</td>
</tr>
</tbody>
</table>
## HPTN 039:
Clinical characteristics of participants

<table>
<thead>
<tr>
<th></th>
<th>Women (n=1380)</th>
<th>Peru MSM (n=1355)</th>
<th>U.S. MSM (n=459)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of anogenital herpes in past 3 months, at enrollment</td>
<td>26%</td>
<td>8%</td>
<td>22%</td>
</tr>
<tr>
<td>Laboratory confirmed STIs, enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis seropositivity</td>
<td>4%</td>
<td>31%</td>
<td>4%</td>
</tr>
<tr>
<td>median titer</td>
<td>1:8</td>
<td>1:4</td>
<td>1:2</td>
</tr>
<tr>
<td>Gonorrhea (cervical /rectal)</td>
<td>0.8%</td>
<td>0.3%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Chlamydia (cervical)</td>
<td>6.0%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Trichomoniasis</td>
<td>8.0%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Pregnancy incidence during study</td>
<td>14%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Male circumcision</td>
<td>--</td>
<td>6%</td>
<td>82%</td>
</tr>
</tbody>
</table>
Time to HIV by study arm

\[ P = 0.39 \]
HIV acquisition events & rate per 100 person-years by gender

<table>
<thead>
<tr>
<th></th>
<th>Acyclovir</th>
<th></th>
<th>Placebo</th>
<th></th>
<th>Total</th>
<th>Rate/100 py</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Rate/100 py</td>
<td>N</td>
<td>Rate/100 py</td>
<td>N</td>
<td>Rate/100 py</td>
</tr>
<tr>
<td>Men</td>
<td>31</td>
<td>3.0</td>
<td>36</td>
<td>3.4</td>
<td>67</td>
<td>3.2</td>
</tr>
<tr>
<td>Women*</td>
<td>44</td>
<td>4.9</td>
<td>28</td>
<td>3.1</td>
<td>72</td>
<td>4.0</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>3.9</td>
<td>64</td>
<td>3.3</td>
<td>139</td>
<td>3.6</td>
</tr>
</tbody>
</table>

**Overall HR 1.16 (95% CI 0.83-1.62)**

*Excluding time off study drug due to pregnancy; HIV incidence in women was 3.8/100 p-yrs (acyclovir) & 3.3/100 p-yrs (placebo)
- Overall HR 1.13 (95% CI 0.81-1.59)
Mean quarterly adherence by pill count & self-report by treatment arm

Consecutive missed doses (≥6) reported at <4% of visits
HIV incidence by level of adherence to the study drug

<table>
<thead>
<tr>
<th>Adherence</th>
<th>Arm</th>
<th>Events</th>
<th>Person-years</th>
<th>Rate per 100 p-yrs</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;90%</td>
<td>Placebo</td>
<td>14</td>
<td>401</td>
<td>3.5</td>
<td>1.6 (0.8, 3.1)</td>
</tr>
<tr>
<td></td>
<td>Acyclovir</td>
<td>22</td>
<td>402</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>&gt;90%</td>
<td>Placebo</td>
<td>44</td>
<td>1364</td>
<td>3.2</td>
<td>1.0 (0.7, 1.6)</td>
</tr>
<tr>
<td></td>
<td>Acyclovir</td>
<td>45</td>
<td>1328</td>
<td>3.4</td>
<td></td>
</tr>
</tbody>
</table>

- For those with >105% adherence or missing data, RR 1.8 (0.4, 7.3)
- Based on Cox model, stratified by site & adjusted for age, GUD at enrollment, & # of SP in past 12 months
Safety of acyclovir – SAE’s

- **63 (4%) in the placebo group**
  - All considered to be unrelated
  - 2 deaths
  - Infections (n=21), trauma (n=12)

- **75 (5%) in the acyclovir group**
  - All considered to be unrelated
  - 6 deaths (inc. 3 traumatic)
  - Infections (n=22), trauma (n=10)
Relative risk of GUD, acyclovir vs. placebo arm, $p<0.001$ for all sites

- Overall, 37% reduction in incidence of GUD in acyclovir arm
- Significant differences in reduction in GUD by region ($p=0.01$)
GUD episodes by study arm

Percent of participants with GUD during study

No. of GUD recurrences during the study

No. of persons

Acyclovir vs Placebo

No. of GUD recurrences during the study
Frequency of HSV detection from genital ulcers during the study

<table>
<thead>
<tr>
<th></th>
<th>Acyclovir N = 729 swabs</th>
<th>Placebo N = 1258 swabs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-2* PCR +</td>
<td>246 (33.7%)</td>
<td>688 (54.7%)**</td>
</tr>
<tr>
<td>Negative</td>
<td>473 (64.9%)</td>
<td>552 (43.9%)</td>
</tr>
<tr>
<td>Inhibited</td>
<td>8 (1.1%)</td>
<td>16 (1.2%)</td>
</tr>
</tbody>
</table>

* Only 2 samples positive for HSV-1 DNA
** p <0.001
Quantity of HSV DNA detected (log10) among HSV positive episodes of genital ulcers, by region

Africa - Placebo

Mean 6.33
N 366
Median 6.66
std 1.5

Africa - Acyclovir

Mean 6.16
N 153
Median 6.45
std 1.45

US - Placebo

Mean 6.03
N 103
Median 6.28
std 1.34

US - Acyclovir

Mean 4.94
N 12
Median 4.34
std 1.63

Peru - Placebo

Mean 6.72
N 221
Median 6.86
std 1.62

Peru - Acyclovir

Mean 6.34
N 83
Median 6.66
std 1.86
Conclusions

• Acyclovir 400 mg bid did not reduce the risk of HIV acquisition among high-risk HSV-2 seropositive MSM and women

• Adherence to study drug was excellent

• Acyclovir 400 mg bid was safe and well-tolerated; largest trial ever of HSV-2 suppression

• Suppressive acyclovir led to a significant reduction in incidence of genital ulcers

• Quantity of HSV-2 detected in ulcers was not reduced in Peru and in Africa
Summary

• Our study is consistent with the Mwanza trial that showed no reduction in HIV acquisition among high risk women treated with acyclovir 400 mg bid

• Surprising, disappointing, and important result for HIV prevention

• Question is whether the lack of efficacy is related to the concept or the intervention
Possible Interpretations

• HSV-2 is not a risk factor for HIV
  ♦ Unlikely to be only confounding, given plethora of epidemiologic data

• HSV in Africa responds less well to acyclovir
  ♦ Less decrease in GUD & HSV quantity in GUD than in prior trials
  ♦ Are acyclovir pharmacokinetics or susceptibility a factor?
  ♦ Was adherence overestimated by pill count & self-report?
  ♦ Other etiologies of genital ulcers also important?

• We have underestimated HSV-2 in terms of frequency of reactivation & genital immune response
  ♦ Need higher doses, new HSV drugs or combination therapy?
  ♦ Need interventions to effectively shut down genital immune response to HSV?
Research Priorities

- HSV-2 interacts with HIV through different mechanisms; should complete studies that are testing different hypotheses
  - HIV transmission (Partners in Prevention)
  - HIV ‘set-point’ (seroconverters in HPTN 039)
  - HIV disease progression (Partners in Prevention, Rakai)

- Biology of HSV-2 in HIV-negative & HIV-positive persons
  - Genital immune activation & persistence
  - Significance of short bursts of HSV shedding

- HSV drugs: new targets, longer duration of activity

- HSV vaccines
Many Thanks to All the Study Participants

Lusaka 039 Participant Support Group
Acyclovir and Valacyclovir Suppression: Similar Effect on GUD Incidence

Reitano JID 1998