

# Herpes Simplex Virus Suppressive Treatment Decreases Plasma and Genital HIV-1 Viral Loads in HSV-2/HIV-1 Co-infected Women: A Randomized, Placebo-Controlled, Cross-Over Trial

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## Background

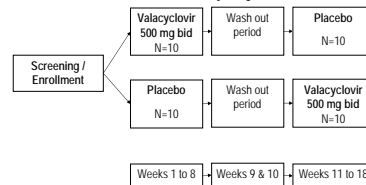
Herpes simplex virus type 2 (HSV-2) is a common co-infection (50-90% prevalence in most populations) among persons with HIV-1. Observational studies have found HSV-2 reactivation to be associated with higher HIV-1 plasma and genital viral loads, suggesting that HSV-2 may increase HIV-1 infectiousness and accelerate disease progression. Our objective was to assess whether HSV-2 suppressive therapy reduces HIV-1 plasma and genital levels.

## Methods

**Study procedures.** Between March and December 2005, we conducted a randomized, double-blind, placebo-controlled, cross-over trial of daily valacyclovir suppressive therapy (500 mg bid) among 20 HSV-2/HIV-1 co-infected women in Lima, Peru.

- |                                 |                                 |
|---------------------------------|---------------------------------|
| <b>Inclusion criteria:</b>      | <b>Exclusion criteria:</b>      |
| • >18 years of age              | • pregnancy                     |
| • HIV-1 & HSV-2 seropositive    | • use of antiretroviral therapy |
| • CD4 count >200 cells/ $\mu$ L | • Cr>2.0 mg/dL, hct<30%         |

### Study design



Field researchers were blinded to the treatment assignments. Medication was dispensed every two weeks, and adherence was assessed by pill counts performed at that time. Study drug was supplied by GlaxoSmithKline (Research Triangle Park, NC). Open label valacyclovir 1 g orally twice daily for three days was dispensed, in addition to study drug, for symptomatic herpes recurrences.

### Samples collected:

- Daily – self-collected anogenital swab for HSV DNA PCR
- Thrice weekly – endocervical swab for HIV-1 RNA PCR
- Weekly – plasma for HIV-1 RNA PCR

## Conclusions

Daily valacyclovir therapy (500 mg twice daily) for HSV-2 suppression significantly reduced plasma and cervical HIV-1 concentrations among HSV-2/HIV-1 co-infected women. Suppressive HSV-2 therapy has the potential to reduce HIV-1 infectiousness and slow the rate of disease progression. These outcomes are under evaluation in ongoing clinical trials.

## Study Population (N=20)

- Median age = 28 years (range 21 to 47)
- Median CD4 count = 372 cells/ $\mu$ L (range 229 to 850)
- 9 had previously taken AZT for PMTCT
  - Last AZT use 84 days prior to study enrollment
- 1 case of syphilis treated prior to enrollment
  - No other STDs detected
- 4 using hormonal contraception; 1 was post-menopausal
- Only 4 had a history of symptomatic genital herpes
  - 3 had previously used acyclovir as treatment during primary genital herpes
  - None had ever used acyclovir for herpes suppression

## Follow-up and Compliance with Study Procedures

**Retention:** All 20 participants finished the study.

**Drug Adherence:** Women took a median of 100% (range 99-100%) of dispensed study medication.

**SAEs:** No serious adverse events were reported, and the study medication was well-tolerated.

**Open label episodic HSV-2 therapy:** 6 women were treated with open-label valacyclovir for herpes recurrences, on a total of 43 study days, of which 31 days were during the placebo period (2.8% of placebo days).

### Compliance with study procedures was high:

- All participants returned 100% of 112 daily self-collected swabs for detection of genital HSV reactivation (2240 swabs in total).
  - 54 swabs (2.4%) could not be analyzed because of PCR inhibition.
- All participants provided once-weekly plasma samples for the entire follow-up period (320 samples in total).
  - 2 samples could not be analyzed.
- Participants provided a median of 46 (range 44-48) of 48 possible thrice-weekly endocervical swab samples for HIV-1 quantification. A total of 933 swabs were collected.
  - 224 (24.0%) could not be analyzed because of PCR inhibition.

## Results

- Valacyclovir significantly reduced genital HSV shedding and plasma and genital HIV-1 concentrations.

### Rates of detection and quantities of genital HSV and plasma and cervical HIV-1, by study arm.

	n/total (%) or mean $\pm$ standard deviation		Difference in quantity <sup>a</sup> (95% confidence interval)	p-value <sup>b</sup>
	Placebo	Valacyclovir		
Genital HSV detection	242 / 1094 (22.1%)	40 / 1092 (3.7%)		<0.001
Genital HSV quantity, <sup>c</sup> log <sub>10</sub> copies/swab	4.80 $\pm$ 1.28	3.94 $\pm$ 1.00	-0.67 (-1.08, -0.26)	0.002
Plasma HIV-1 viral load, log <sub>10</sub> copies/mL	4.60 $\pm$ 0.76	4.34 $\pm$ 1.01	-0.27 (-0.34, -0.20)	<0.001
Cervical HIV-1 detection	266 / 374 (71.1%)	182 / 335 (54.3%)		<0.001
Cervical HIV-1 viral load, log <sub>10</sub> copies/swab	3.31 $\pm$ 1.11	2.93 $\pm$ 1.06	-0.35 (-0.46, -0.25)	<0.001

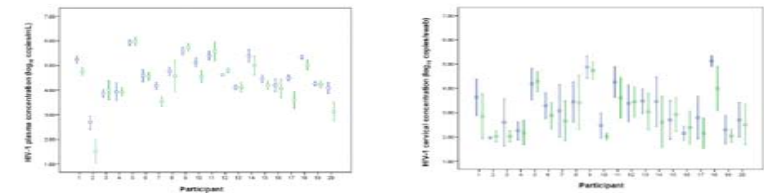
<sup>a</sup> For continuous measures, average differences in quantity between the study arms from linear mixed-effects models. P-values are from generalized estimating equations models for dichotomous measures and from linear mixed-effects models for continuous measures.

<sup>b</sup> Among those with detectable genital HSV.

- The difference in HIV-1 concentrations, by linear mixed-effects analysis, represented a 54% and 55% decrease in plasma and genital HIV-1 concentrations, respectively.

- Most HSV shedding was asymptomatic: women reported genital ulcers on only 23 (2.1%) valacyclovir days and 49 (4.6%) placebo days.

*HIV-1 concentrations in plasma (left panel) and cervical (right panel) samples, for each study participant, stratified by treatment arm (blue = placebo, green = valacyclovir). Circles represent the mean and brackets indicate 1 SD.*



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