Impact of Herpes Suppression on Genital Immunology

Tae Joon Yi

Supervisor: Dr. Rupert Kaul

HIV

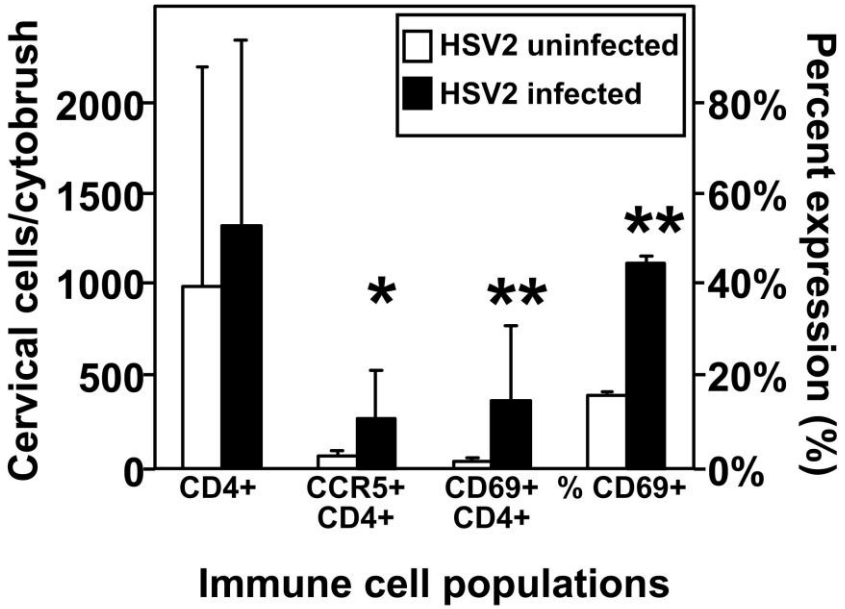
- 33 million people living with HIV
- Women account for more than 50%
- The primary route of HIV transmission is sexual
  - However, >99% of sexual exposures to HIV do not result in infection
- Sexually transmitted infections (STIs) increase the risk of acquiring HIV
  - Herpes simplex virus 2 has been associated with 3-6 fold increase in HIV acquisition

Herpes Simplex Virus

- Two types of herpes simplex virus (HSV)
  - Enveloped DNA virus that causes lifelong infection
  - HSV-1 – outbreaks mostly occur on the lips
  - HSV-2 – outbreaks mostly occur on the genitals
- Most cases of both have no symptoms (80%)
- Prevalence of HSV-2
  - >60% of adults are infected in Africa
  - ~20% of adults are infected in North America
  - Within any age stratum – women at more risk

HSV-2

- May have increased number of CD4+ T cells in the cervix of HSV-2+ women, even when no reactivation



Rebbapragada et al. AIDS 2007

Clinical Trials

- Major clinical trials looking at HIV acquisition
  - Suppressive acyclovir did not decrease HIV acquisition in HSV-2+ individuals (2 RCTs)
  - Sample sizes of 821 and 3172

- Possible reasons:
  - The long lasting mucosal immune effects and sub-optimal suppressive efficacy
  - Suppression cannot reverse HSV2-associated increases in target cells

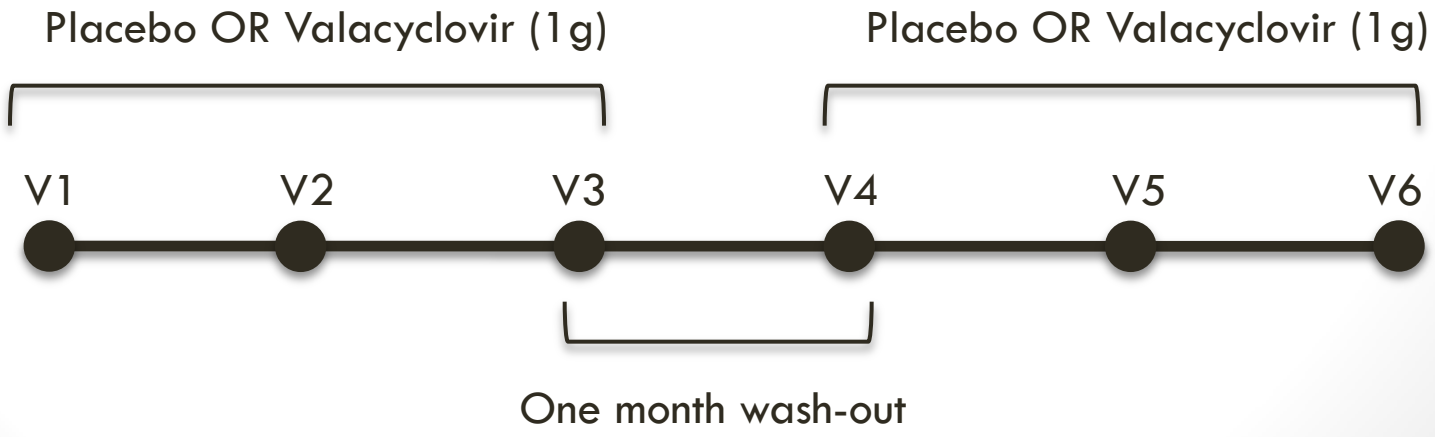
Overall

- HSV-2 is associated with 3 fold increase in HIV acquisition
  - May relate to increased HIV target cells in the cervix

- Valacyclovir may be more potent than acyclovir
  - Possible reason for failure of the RCTs to reduce HIV
  - Once daily valacyclovir dosing may improve compliance
  - But even non-approved, super-high VAL doses only able to reduce HSV2 reactivation to 1/30 days
  - Is that effective enough to reduce mucosal susceptibility?

Study Hypothesis and Design

- Valacyclovir therapy in HSV-2+ HIV- women will reduce the number of HIV target cells in the endocervix
  - Aim: To elucidate the impact of valacyclovir on genital HIV target cells and mucosal inflammation in HIV uninfected women.
- Double-blinded placebo controlled crossover trial in HSV-2+ HIV- women from Toronto African / Caribbean community
- Performed at Women's Health in Women's Hands clinic



Study Endpoints

- Primary endpoints – change in the number of cervical CD4+ T cells during valacyclovir vs. placebo phase

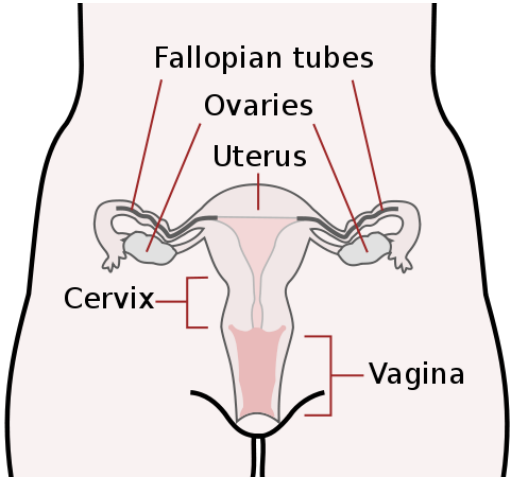
- Secondary endpoints:
  1. Change in the number of several T cell and dendritic cell (DC) subsets during valacyclovir vs. placebo phase
  2. Change in cervico-vaginal cytokines during valacyclovir vs. placebo phase
  3. Self-reported medication compliance

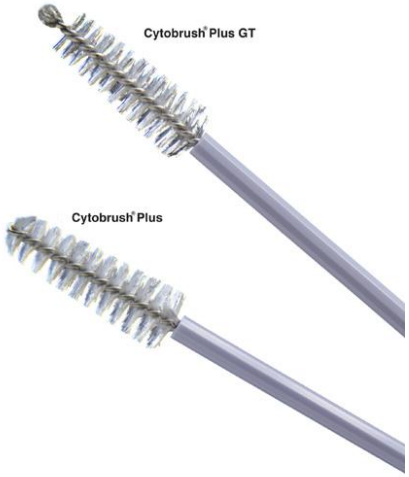
- Sample size considerations: based on a previous study we can detect a difference of 0.31 log10 DCs with N=30

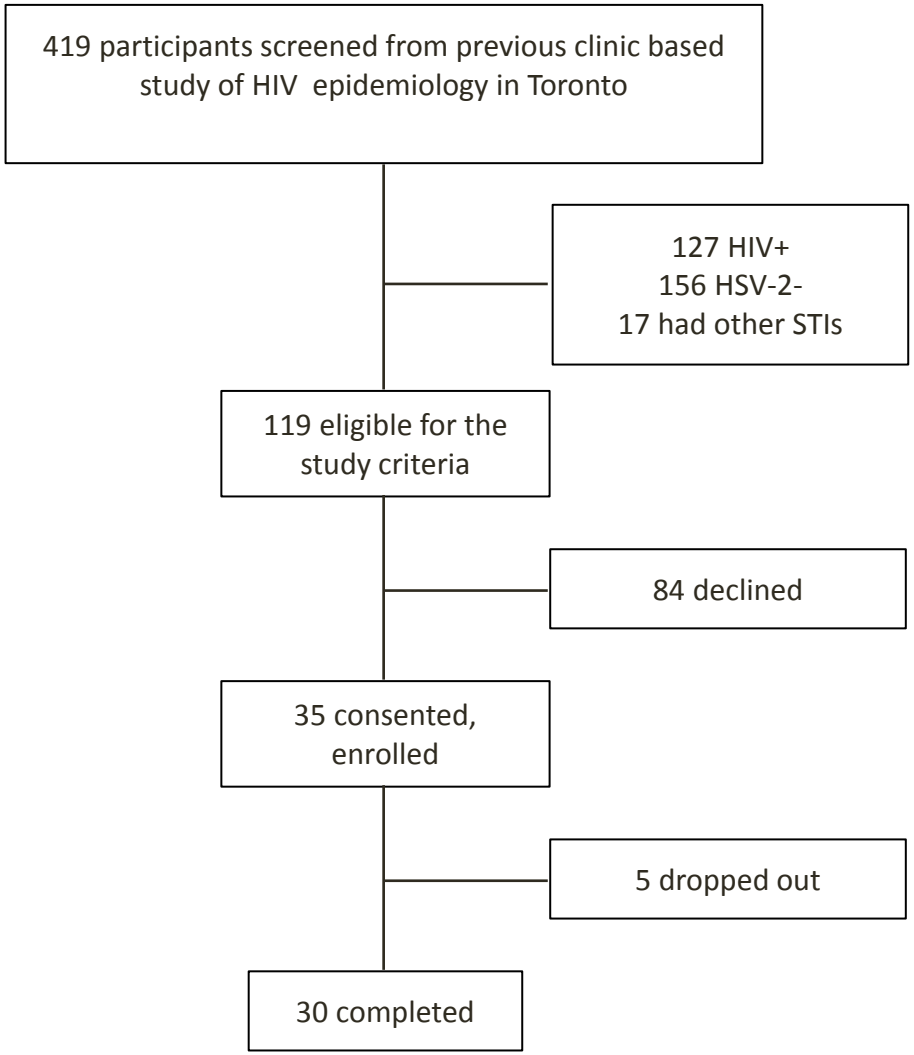
Study Design

- At each visit, STI diagnostics were done.
  - Gon, Trich, Chla, BV (gram stain)

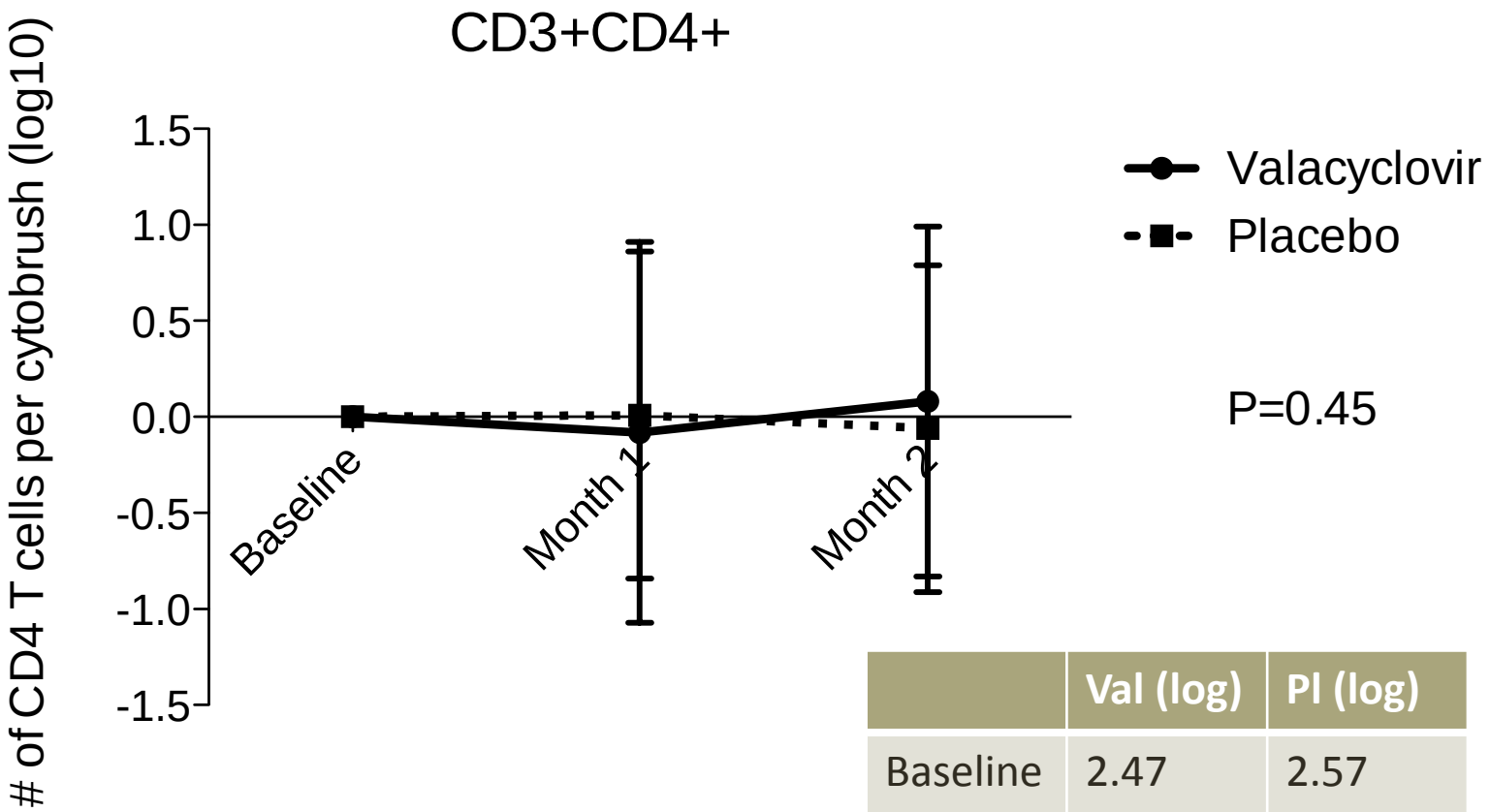
- Immune studies
  - Two pooled cytobrushes for T cell and DC panels
  - Instead cup to collect cervico-vaginal secretions for cytokine analysis





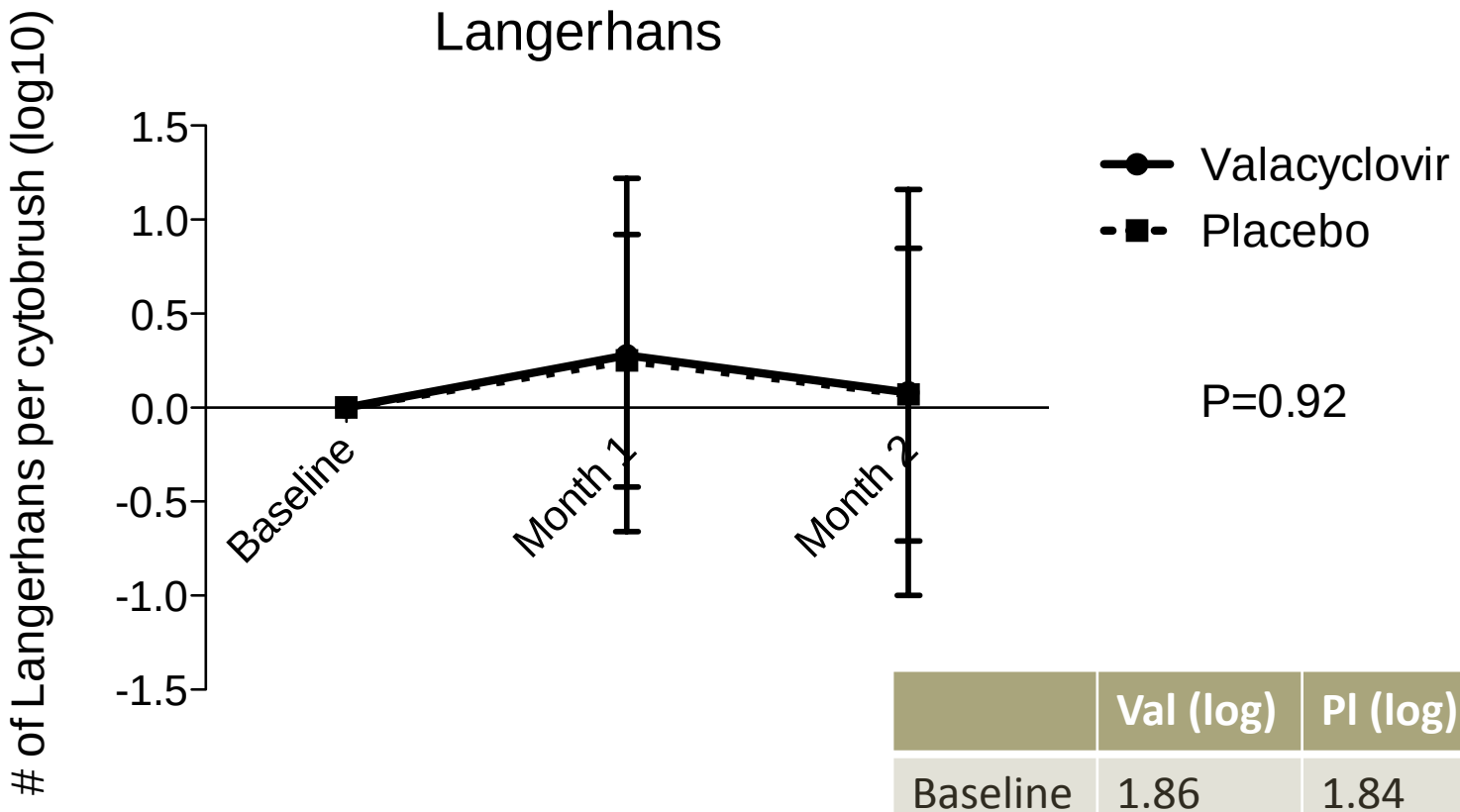

419 participants screened from previous clinic based study of HIV epidemiology in Toronto
127 HIV+
156 HSV-2-
17 had other STIs
119 eligible for the study criteria
84 declined
35 consented, enrolled
5 dropped out
30 completed

Results: primary endpoint



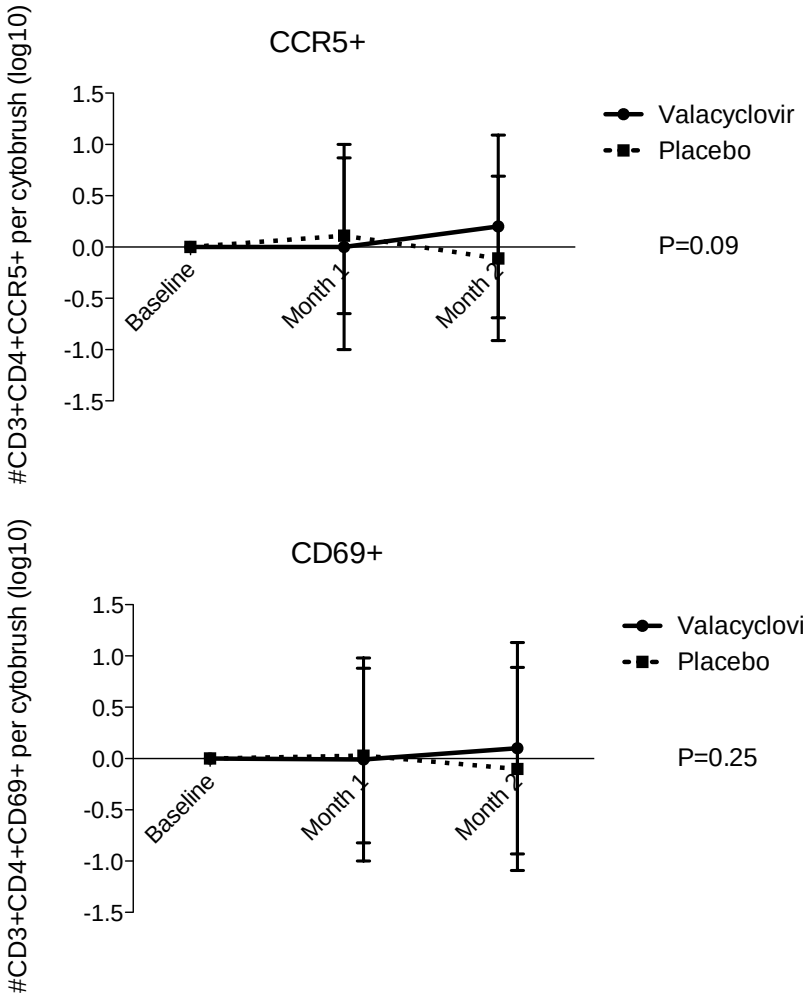
	Val (log)	Pl (log)
Baseline	2.47	2.57
V2-BL	-0.08	0.01
V3-BL	0.08	-0.06

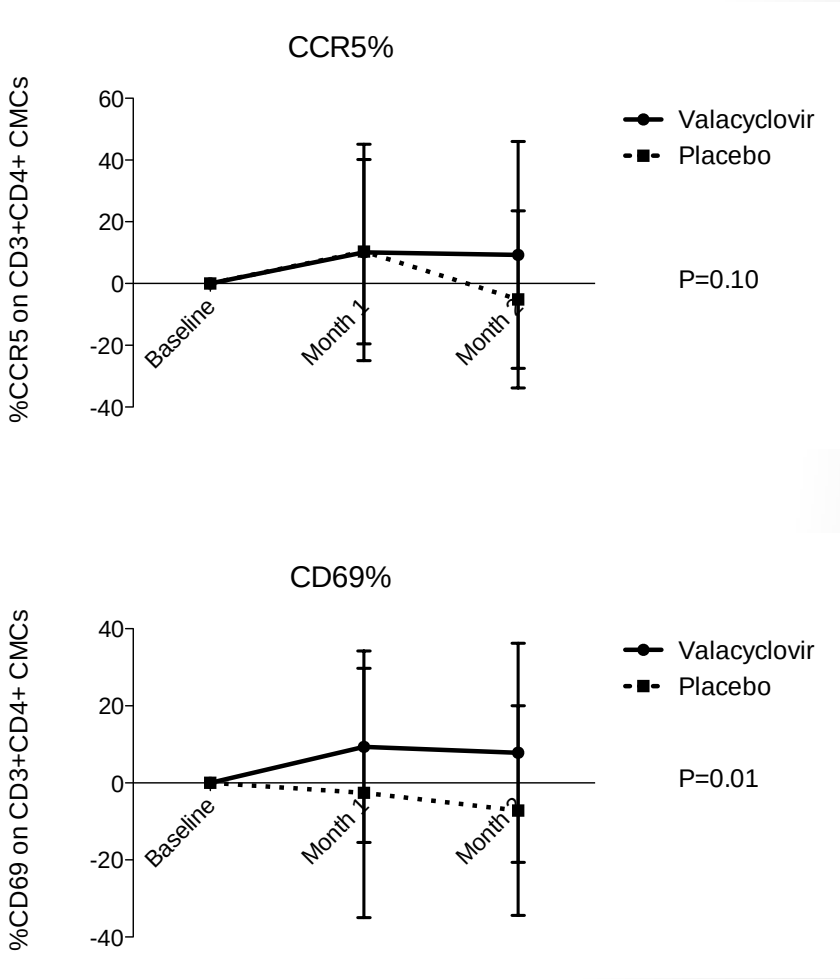
Results: secondary endpoints



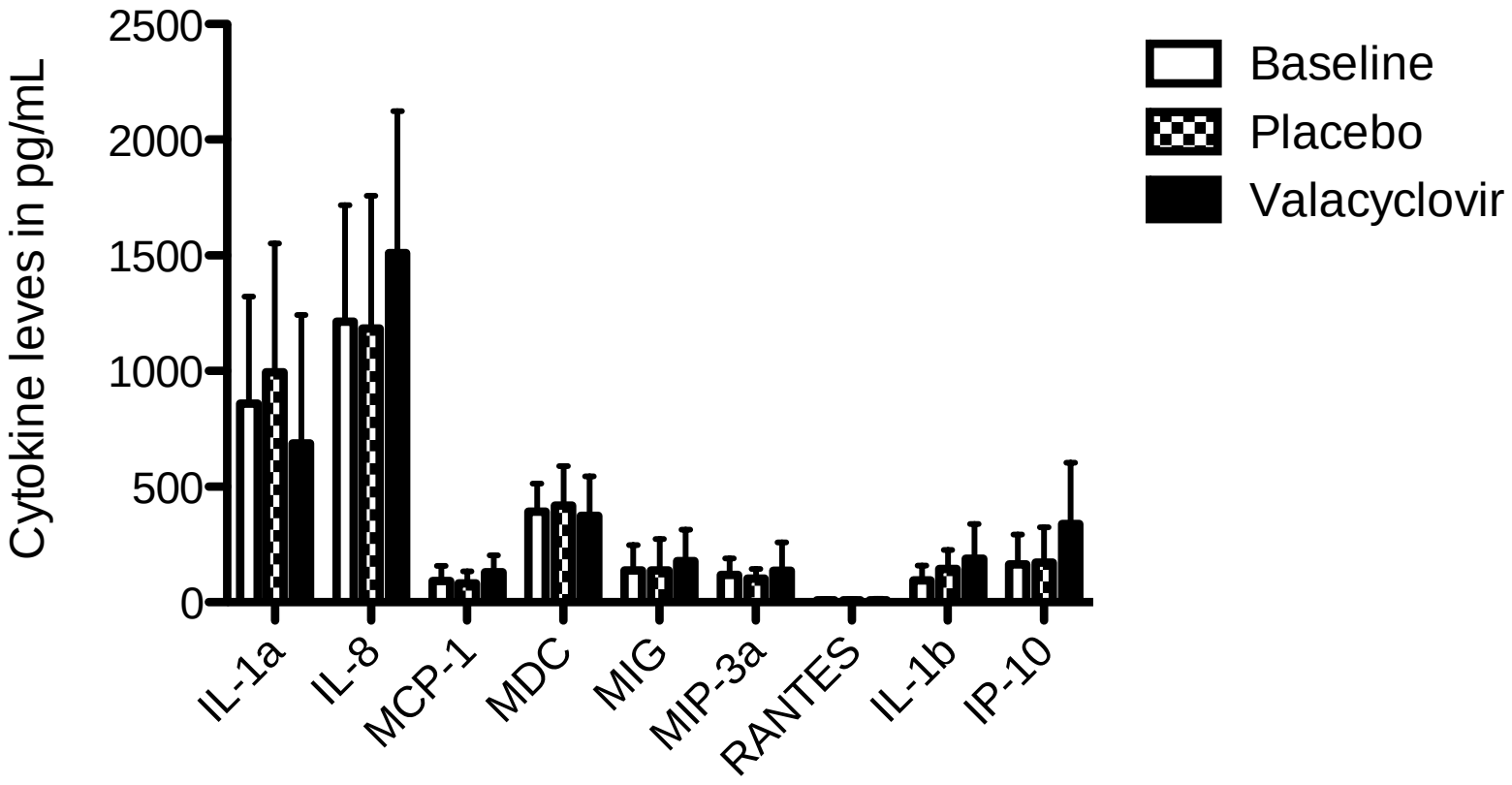
	Val (log)	Pl (log)
Baseline	1.86	1.84
V2-BL	0.28	0.25
V3-BL	0.08	0.07

Results: secondary endpoints





Results


Cytokine leves in pg/mL
2500
2000
1500
1000
500
0
IL-1a
IL-8
MCP-1
MDC
MIG
MIP-3a
RANTES
IL-1b
IP-10
Baseline
Placebo
Valacyclovir

Conclusion

- Two months of valacyclovir had no effect on CD4+ T cells numbers in the cervix
- In secondary analyses, there was an increased expression of CD69 (P=0.01) and a trend to an increase in CCR5 expression (P=0.10) during valacyclovir therapy
- Significance was lost when controlled for period and carryover effects
- No significant impact on genital cytokines, other T cell subsets, or DC subsets

Discussion

- Overall, no change in the absolute number of cervical CD4+ T cells
- Supports results of clinical trials, despite using more potent valacyclovir
- Increase in CD69 and CCR5 expression:
  - Caused by host immune response after HSV-2 suppression?
  - Short term therapy – would it be lowered in the longer term?
  - Other STIs have long lasting effects

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Brett Shannon
Vineet Joag

Committee Members:
Dr. Sharon Walmsley
Dr. Dana Philpott

Dr. Darrell Tan

Statisticians:
Dr. Janet Raboud
Dr. DeSheng Su

WHIWH:
Lisungu Chieza
Dr. Megan Saunders

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