

HPTN 035 Placebo

Goal: A “non-perturbing” placebo
(neither protective nor harmful)

Background

- ◆ Question raised of whether result of COL1492 trial of N9 was influenced by use of a placebo with protective activity
 - Placebo was Replens®, an acid-buffering gel
- ◆ Thus, a significant effort was made to design and thoroughly test a “non-perturbing” placebo for HPTN 035

Designed to lack anti-HIV effect

- ◆ Uncharged gelling agent
 - Avoids polyanions with anti-HIV activity
 - Avoids mechanical protection of high yield-strength
- ◆ Minimal buffering power
 - Will not acidify semen
- ◆ Sorbic acid preservative
 - Preservative demonstrated non-virucidal

Designed to minimize effect on epithelium and flora

- ◆ Sorbic acid preservative
 - Non-inflammatory
 - Metabolized by human cells
- ◆ Isotonic
 - Neither dehydrates or swells epithelium
 - Does not thin and drip out
- ◆ Minimal metabolizable substrates that might alter flora
- ◆ Formulated at vaginal pH
 - But with minimal buffer capacity

Formula

- ◆ 96% purified water
- ◆ 2.7% hydroxyethylcellulose gelling agent
- ◆ 0.1% sorbic acid
- ◆ 0.85% sodium chloride
- ◆ pH adjusted to 4.4 with sodium hydroxide
(vaginal pH, but minimal buffer capacity)

“K-Y Jelly with several potentially problematic components removed.”

Tests of HPTN 035 placebo

- ◆ No inactivation of HIV *in vitro*
- ◆ No protection in SHIV/macaque model
(4/7 infected with HPTN 035 placebo, 3/7 infected with no pretreatment)
- ◆ No protection in HSV-2/mouse model
(9/10 infected after HPTN 035 placebo, 8/10 after no pretreatment)
- ◆ No increase in post-exposure susceptibility to HSV-2
(In contrast, 20-30-fold increased susceptibility observed after detergents)
- ◆ No acidification of semen
- ◆ No spermicidal effect
- ◆ No cytokine induction from vaginal epithelial cell line
- ◆ Well tolerated and acceptable in a Phase I trial

Conclusion

The HPTN 035 Placebo has been carefully designed and extensively tested and appears to be a “neutral placebo”.