

Title: Assessing Markers of Inflammation after Vaginal Product Use: Nonoxynol-9, Cellulose Sulfate, and HEC Placebo Comparative Double-Blind Phase I Trial

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Background: Cellulose sulfate (CS) did not prevent and may have increased the risk of HIV in one trial. The present study was done to investigate established and new vaginal Phase I safety markers in an effort to better understand Phase III results and determine which markers may be most useful in future studies.

Methods: Sixty women were randomized to use nonoxynol-9 (N9), CS, or a hydroxyethyl cellulose placebo (HEC) vaginal gel twice daily for 2 weeks. Endpoints were assessed before use, after 1 week, and 8-18h and 58-66h after the last dose. Established endpoints included adverse events, colposcopic findings, microflora changes, and soluble markers in cervicovaginal lavage (CVL). Exploratory endpoints included cellular markers in CVL and biopsy, histopathology, and anti-HIV activity of CVL. Natural-log-transformed soluble marker data were modeled by individual clinical variables, gel, center, and visit using mixed models (visit as repeated measure). Due to baseline variability, change-from-baseline scores were calculated.

Results: CS was associated with decreased MPO and IL-1RA levels compared with HEC, controlling for clinical variables, center, and visit. CD45+ and CD68+ cell counts in CVL pellets were lower with CS than HEC. Change scores for IL-8, MPO, and SLPI were lower for CS than HEC and change scores for *E.coli* and *Enterococcus* were higher. Anti-HIV activity of CS was maintained during dosing. N9 was associated with increased IL-1 α , IL-1 β , IL-8, and MPO levels compared with HEC, controlling for most clinical variables, center, and visit. Change scores for IL-1 α , IL-1 β , IL-1RA, IL-8, MPO, and anaerobic gram negative rods were higher for N9 than HEC, and SLPI was lower. Among the two women with inflammation seen by biopsy, levels of IL-1 α , IL-1 β , IL-1RA, and MPO were 9-23 times higher than for women without, controlling for gel, center, and visit. Colposcopic epithelial disruption or findings >1cm were associated with 2-6 times higher levels of IL-1 α , IL-1 β , IL-6, IL-8, and MPO and lower SLPI levels.

Conclusions: N9 was associated with an inflammatory pattern of results, but CS was not. CS exposed to the vaginal environment retained its anti-HIV activity. The importance of the microflora changes seen with CS is unclear. Certain markers obtained via CVL may indicate inflammation seen using biopsies which are more invasive. Epithelial disruption and large colposcopic findings also appear to be associated with increased inflammatory markers.