Poster 871

Phase I Trial to Assess Safety, PK, and PD of Film and Gel Formulations of Tenofovir

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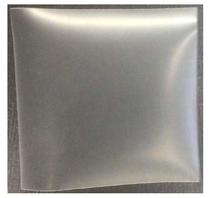
Background

- Fast dissolving vaginal film formulations of topical microbicides may provide more efficient vaginal drug delivery than gels because films dissolve directly into vaginal fluid.
- Tenofovir (TFV) films are 2"x2 " cellulose based vaginal films. The films are soft, flexible, and translucent.

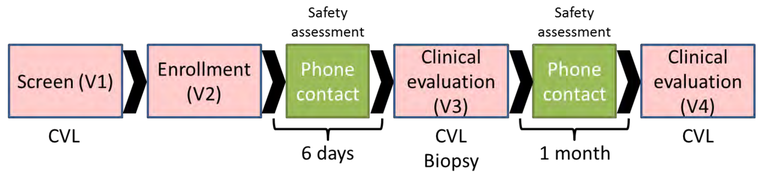


- In this first in human Phase 1 study of vaginally applied tenofovir films, the safety, pharmacokinetics, and pharmacodynamics of 1% tenofovir gel and two doses of tenofovir film were compared to matched placebo..

Methods

- HIV negative women were randomized to 1 of 5 groups.
  - Film: 10 mg film, 40 mg film, or placebo film
  - Gel: 4 mL of 1% tenofovir gel (40mg) or HEC placebo gel
- 1st dose in clinic, 6 doses at home, 7th timed delivery in clinic

Figure 1. Study Schema



- Adverse event (AE): collected via questionnaire and exam. The incidence of grade 2 related AEs was compared across arms.
- Pharmacokinetics:
  - Plasma and rectal fluid tenofovir were measured before and 2 h after last product use.
  - Tenofovir-diphosphate levels were measured in cervical and vaginal tissue biopsies obtained 2 h after last product use.
- Pharmacodynamics: Cervical biopsies were exposed to HIV-1 in an *ex vivo* challenge assay. Tissue HIV infection was monitored by p24 levels in culture supernatants for active vs. placebo products.

Results

- Study population: 78 women enrolled; 75 evaluable.
  - Median age 28.0 yr; 73% white; 79% some college education
- Safety: 1 grade 2 or higher related AE for vaginal pain in the tenofovir gel group; no difference in the rate of urogenital AEs amongst the five groups.

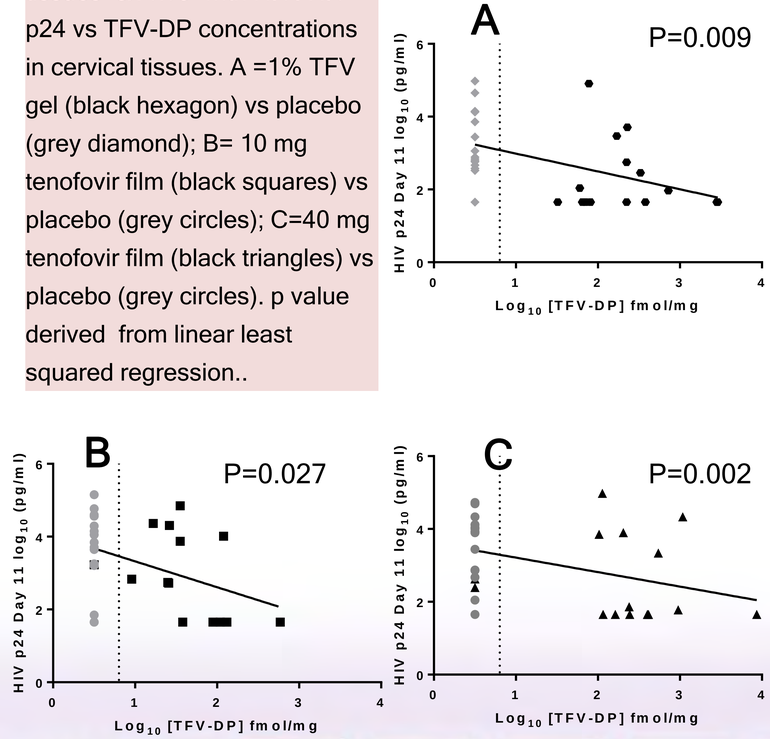
Table 1. Median tenofovir (TFV) concentration in plasma and rectal fluid. 10mg TVF film and TVF gel were compared to 40mg TVF film. *p<0.05

Tenofovir ng/mL	1% TFV Gel (n=15)	10 mg Film (n=14)	40 mg Film (n=16)
Plasma TFV after 6 doses	0.56 (0.00,3.46)	0.40 (0.00, 2.81)*	1.89 (0.00, 5.45)
Plasma TFV 2 hrs after 7th dose	2.33 (0.00,13.00)	0.98 (0.00, 2.27)*	2.55 (0.00, 9.78)
Rectal fluid TFV 2 hrs after 7th dose	31.07 (1.65,3689)	14.90 (0.73, 267)	33.99 (2.76, 1933)

Table 2. Median tenofovir-diphosphate (TFV-DP) levels in genital tissues. 10 mg TVF film and TVF gel were compared to 40mg TVF film. *p<0.05

	1% TFV Gel (n=15)	10 mg Film (n=14)	40 mg Film (n=16)
Cervical tissue (ng/mL)	222 (32, 2888)	35 (0, 590)*	816 (0, 8411)
Vaginal tissue (ng/mL)	296 (45, 2114)	50 (0, 1179)	243 (0, 8647)

Figure 2. Challenge of cervical tissues *ex vivo* with HIV. HIV p24 vs TFV-DP concentrations in cervical tissues. A =1% TFV gel (black hexagon) vs placebo (grey diamond); B= 10 mg tenofovir film (black squares) vs placebo (grey circles); C=40 mg tenofovir film (black triangles) vs placebo (grey circles). p value derived from linear least squared regression..



- Acceptability:
  - 53% of participants reported that the film was easy to insert.
  - Film users were less likely to report product leakage than gel users (67% vs 100%, P<0.001), and film users were less likely to report any discomfort after insertion than gel users (18% vs 43%, P=0.02).
- Future use: 60% of film users and 67% of gel users reported that they would be likely to use the product should it be found effective against HIV.

Conclusions

- Both doses of the tenofovir film and the 1% gel were well tolerated.
- The 40-mg tenofovir film group yielded comparable tenofovir concentrations in plasma and genital tissue when compared to gel.
- Tenofovir film and gel reduced HIV replication in cervical tissue.
- Women reported that film use resulted in less product leakage than gel.
- Film technology for the delivery of antiretrovirals is a promising efficient, low cost, and tolerable formulation .

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FILM ANTIRETROVIRAL MICROBICIDE EVALUATION