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# Does Tenofovir Gel alter HIV Disease Progression in CAPRISA 004 Trial Seroconvertors?

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## Background

- Pre-exposure prophylaxis (PrEP) prevents HIV acquisition in MSM[1], intravenous drug users[2] and heterosexual men and women[3, 4].
- However, currently it is not known whether PrEP may alter HIV disease progression in seroconvertors.
- Previous studies of seroconvertors from CAPRISA 004[5], a phase IIb trial assessing safety and effectiveness of the vaginal microbicide 1% tenofovir (TFV) gel, have shown that:
  - the diversity of the transmitting virus was similar between seroconvertors from the TFV and placebo arms[6].
  - T cell responses were preserved during early infection despite exposure to PrEP[7].
  - sensitive drug resistance screening of plasma and cervical specimen collected during acute HIV infection did not reveal any PrEP-related TFV drug resistance mutations[8].

## Objectives

- This study assessed whether TFV gel use impacted on disease progression among CAPRISA 004 seroconvertors.

## Methods

- CAPRISA 004 Microbicide Trial seroconvertors were followed up prospectively in the CAPRISA 002 Acute Infection Study.
- Disease progression was assessed by viral load (VL), CD4 count and need for antiretroviral therapy (ART) (CD4<350).
- Linear mixed models were fitted to CD4 and VL measurements within 2 years of infection.
- Participants reaching CD4<350 cells/ul were compared by log rank test.

## Results

### Study Population

- 83 of 98 (84.7%) CAPRISA 004 seroconvertors consented to participate in the CAPRISA 002 Acute Infection Study contributing 296 women-years of follow-up.
- 32 had been assigned to TFV gel, 51 to placebo in CAPRISA 004.
- Study population characteristics are summarized in Table 1.

**Table 1: Baseline characteristics of CAPRISA 004 seroconvertors enrolled into the CAPRISA 002 Acute Infection Study**

| Characteristic | All (N=83) | Tenofovir arm (n=32) | Placebo arm (n=51) | p-value† |
|---|---|---|---|---|
| Median age at seroconversion in years (IQR) | 22 (21 – 25) | 23 (20 – 27) | 22 (21 – 25) | 0.460 |
| % Rural (n) | 67.5% (56) | 65.6% (21) | 68.6% (35) | 0.813 |
| % sexual partners prior to seroconversion | | | | |
| More than one | 1.2% (1) | 0.0% (0) | 2.0% (1) | 0.690 |
| One only | 81.9% (68) | 78.1% (25) | 84.3% (43) | |
| None | 16.9% (14) | 21.9% (7) | 13.7% (7) | |
| Median number of sex acts in past 30 days at visit prior to seroconversion (IQR) | 4 (2 – 7) | 3 (2 – 5) | 5 (2 – 7) | 0.082 |
| Median number of returned used gels at visit prior to seroconversion (IQR) | 6 (3 – 10) | 5 (2 – 10) | 8 (4 – 10) | 0.287 |
| Median adherence in 004 (IQR) | 59.2% (50 – 100%) | 56.7% (50 – 100%) | 60.0% (50 – 100%) | 0.927 |
| % with condom use at last sex at reported at visit prior to seroconversion (n) | 84.2% (69) | 81.3% (26) | 86.0% (43) | 0.758 |
| % on Depo-Provera at end of 004 trial (n) | 61.5% (51) | 59.4% (19) | 62.8% (32) | 0.819 |
| % with any STI symptoms within 3 months prior to seroconversion (n) | 32.5% (27) | 34.4% (11) | 31.4% (16) | 0.813 |
| HSV-2 status during 004 trial | | | | |
| % Baseline Positive (n) | 56.6% (47) | 53.1% (17) | 58.8% (30) | 0.866 |
| % Stayed Negative (n) | 24.1% (20) | 25.0% (8) | 23.5% (12) | |
| % Became Positive (n) | 19.3% (16) | 21.9% (7) | 17.7% (9) | |
| Median estimated days post infection at CAP002 enrolment (IQR) | 37 (24 – 65) | 40 (29 – 83) | 36 (22 – 59) | 0.133 |
| % BV at CAP002 enrolment* (n) | 55.6% (45/81) | 62.5% (20) | 51.0% (25/49) | 0.365 |
| % T. vaginalis at CAP002 enrolment* (n) | 4.9% (4/81) | 9.4% (3) | 2.0% (1/49) | 0.295 |
| % N. gonorrhoea at CAP002 enrolment* (n) | 6.2% (5/81) | 3.1% (1) | 8.2% (4/49) | 0.643 |
| % C. trachomatis at CAP002 enrolment* (n) | 16.1% (13/81) | 18.8% (6) | 14.3% (7/49) | 0.758 |
| % M. genitalium at CAP002 enrolment* (n) | 8.6% (7/81) | 12.5% (4) | 6.1% (3/49) | 0.426 |
| % HSV-2 PCR at CAP002 enrolment* (n) | 11.1% (9/81) | 12.5% (4) | 10.2% (5/49) | 0.734 |
| % with any STI** at CAP002 enrolment excluding BV (n) | 40.7% (33/81) | 43.8% (14) | 38.8% (19/49) | 0.817 |
| Median first viral load after HIV infection in 004 (copies/ml) (IQR) | 4.60 (3.75-5.25) | 4.74 (3.97-5.37) | 4.45 (3.56-5.17) | 0.189 |
| Median weeks post infection at first viral load in 004 (IQR) | 2 (2 – 2) | 2 (2 – 3) | 2 (2 – 2) | 0.224 |
| Median first CD4 count after HIV infection (IQR) | 498 (393 – 643) | 467 (380 – 530) | 519 (414 – 689) | 0.106 |
| Median weeks post infection at first CD4 count (IQR) | 5 (3 – 9) | 6 (4 – 12) | 5 (3 – 8) | 0.159 |

†p-value calculated using Wilcoxon rank sums test (medians) or Fisher's exact tests (proportions).
*Bacterial vaginosis (BV) Missing STI data at CAPRISA 002 enrolment for 2 participants from the placebo arm.
** Any STI defined as having either T. vaginalis, N. gonorrhoeae, C. trachomatis, M. genitalium, HSV-2 PCR or syphilis

### Viral load & CD4 count results

- Median 2-week post-infection VL was 4.74 and 4.45 log copies/ml in women assigned to TFV and placebo (p=0.189).
- Corresponding 12-month post-infection median VLs were 4.24 and 3.70 log copies/ml (p=0.016).
- VL and CD4 results are summarized in Figure 1 and Table 2.

**Figure 1: Scatterplot of viral load measurements within the first two years of HIV infection, with a Loess smoothing line, stratified by CAPRISA 004 1% tenofovir gel and placebo arms**

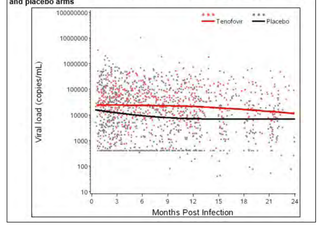



**Table 2: Comparison of HIV viral load and CD4 count at 3-monthly intervals post-infection**

| Month | | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 |
|---|---|---|---|---|---|---|---|---|---|
| **Viral load (log copies/ml)** | | | | | | | | | |
| Tenofovir | n | 28 | 31 | 30 | 30 | 29 | 26 | 26 | 22 |
| | Median (IQR) | 4.42 (3.74 - 4.91) | 4.69 (3.84 - 4.99) | 4.46 (3.98 - 4.89) | 4.24 (3.75 - 4.77) | 4.23 (3.55 - 4.81) | 4.21 (3.49 - 4.88) | 3.96 (3.51 - 4.62) | 4.10 (3.46 - 4.86) |
| Placebo | n | 45 | 47 | 46 | 46 | 43 | 37 | 41 | 33 |
| | Median (IQR) | 4.03 (3.08 - 4.84) | 4.12 (3.13 - 4.95) | 4.08 (2.92 - 4.66) | 3.70 (2.60 - 4.66) | 3.88 (3.23 - 4.56) | 3.69 (3.19 - 4.55) | 3.76 (3.18 - 4.44) | 3.55 (3.12 - 4.58) |
| p-value* | | 0.154 | 0.055 | 0.055 | **0.016** | 0.189 | 0.122 | 0.351 | 0.189 |
| **CD4 count (cells/µl)** | | | | | | | | | |
| Tenofovir | n | 28 | 30 | 30 | 30 | 29 | 26 | 26 | 22 |
| | Median (IQR) | 492 (391 - 631) | 471 (365 - 602) | 443 (393 - 606) | 442 (301 - 578) | 434 (325 - 531) | 476 (367 - 679) | 477 (396 - 592) | 454 (412 - 640) |
| Placebo | n | 45 | 47 | 46 | 46 | 43 | 39 | 42 | 34 |
| | Median (IQR) | 537 (433 - 683) | 487 (374 - 737) | 461 (365 - 672) | 432 (368 - 655) | 480 (352 - 641) | 513 (409 - 653) | 536 (392 - 591) | 510 (374 - 626) |
| p-value* | | 0.475 | 0.487 | 0.629 | 0.323 | 0.181 | 0.512 | 0.331 | 1.000 |

*Wilcoxon rank sums test

### Adjusted viral load model

- After adjusting for clinical and behavioural characteristics and HLA haplotype, overall mean VLs were 4.51 and 4.02 log copies/ml (TFV vs placebo arm, p=0.013) (Table 3).
- Corresponding mean CD4 counts were 463 and 514 cells/µl (p=0.290).

**Table 3: Univariate and multivariate linear mixed model fitted to HIV viral load within the first 24 months infection**

| Variable | Univariate analysis* | | Multivariate analysis | |
|---|---|---|---|---|
| | Effect estimate (SE) | p-value | Effect estimate (SE) | p-value |
| Tenofovir vs Placebo | 0.38 (0.20) | 0.059 | 0.50 (0.20) | **0.013** |
| Age in years | -0.02 (0.02) | 0.373 | -0.02 (0.03) | 0.438 |
| Rural vs urban site | 0.25 (0.21) | 0.229 | 0.08 (0.26) | 0.745 |
| DMPA vs no DMPA** | 0.16 (0.20) | 0.423 | 0.40 (0.23) | 0.084 |
| Condom used at last sex act ** No vs Yes | 0.42 (0.27) | 0.127 | 0.49 (0.28) | 0.078 |
| Number of sexual partners** | 0.29 (0.25) | 0.244 | 0.39 (0.34) | 0.255 |
| Number of returned used applicators** | -0.01 (0.02) | 0.519 | -0.10 (0.05) | 0.058 |
| Number of sex acts in the last 30 days** | 0.01 (0.02) | 0.578 | 0.09 (0.05) | 0.079 |
| Median gel adherence in 004 | -0.003 (0.004) | 0.4436 | 0.003 (0.005) | 0.636 |
| STI symptoms within 3 months prior to seroconversion† Yes vs No | -0.12 (0.21) | 0.562 | -0.22 (0.23) | 0.333 |
| HSV2 status in 004 | | | | |
| Baseline positive vs remained negative | -0.04 (0.24) | 0.857 | -0.002 (0.26) | 0.995 |
| Became positive vs remained negative | 0.49 (0.30) | 0.106 | 0.40 (0.31) | 0.197 |
| Bacterial vaginosis at 002 enrolment positive vs negative | -0.04 (0.20) | 0.844 | -0.14 (0.22) | 0.511 |
| Any STI# at 002 enrolment Yes vs No | -0.11 (0.20) | 0.598 | -0.36 (0.22) | 0.094 |
| Protective HLA-B type¥ Yes vs No | -0.47 (0.22) | 0.036 | -0.35 (0.23) | 0.141 |

*All univariate analyses were adjusted for time post infection and viral load assay used (Taqman1 vs Amplicor)
**As reported at last visit prior to HIV infection in 004
†STI symptoms defined as having any Cervicitis, Genital discharge, Pelvic inflammatory disease, Sexually transmitted disease, Trichomoniasis, Uterine cervix ulcer, Vaginal discharge, Vaginal pain, Vulval oedema
#Any STI is defined as having either T. vaginalis, N. gonorrhoea, C. trachomatis, M. genitalium, HSV-2 PCR or syphilis.
¥ Protective HLA-B types defined as B*1302, B*27, B*57, B*5801, B*1801, harmful HLA-B types are B*1801, B*35, B5802

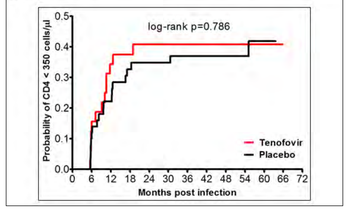
### Tenofovir gel levels and VL

- Among women assigned to TFV gel, overall mean VLs were 4.53 and 4.60 log copies/ml in women with detectable versus undetectable TFV levels (p=0.840).

### Need for ART

- 32 (38.6%) women reached a CD4 count <350 cells/ul at median 9.4 months post-infection, 13 (40.6%) from the TFV and 19 (37.3%) from the placebo arms (p=0.786) (Figure 2).

**Figure 2: Kaplan-Meier graph of time to CD4 count <350 cells/µl stratified by CAPRISA 004 arm**




## Discussion

- TFV gel had no impact on post-infection CD4 counts or time to ART initiation (CD4<350).
- TVF levels during CAPRISA 004 were not associated with post-infection VL.
- Significant differences in post-infection VLs were detected and were only partially explained by cohort variability and protective haplotypes.
- An important limitation of the study was that women were no longer randomized once enrolled into the CAPRISA 002 Acute Infection study and remaining confounders may not have been included in the analysis.
- Whether the difference in VL could have occurred due to a delayed antibody response because of PrEP still needs be determined.

## Conclusion

- Despite an increased 12-month viral load in CAPRISA 004 seroconvertors from the TFV gel PrEP arm, there was no difference in disease progression in this cohort.

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