

Higher Colorectal Tissue HIV Infectivity in HIV seronegative CGW Compared to MSM With & Without Oral PrEP – HPTN 069 sub-study

Sekabira, et al. AIDS 2021

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 HPTN
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Background

- HPTN 069 randomized men & women without HIV to daily oral candidate and control PrEP regimens for 48 weeks:
 - Maraviroc (MVC) only
 - MVC+ Emtricitabine (FTC)
 - MVC+ Tenofovir disoproxil fumarate (TDF)
 - TDF+FTC (PrEP control regimen)
- PrEP
Candidate
Regimens*
- Ex vivo tissue challenge with HIV is frequently used to assess readiness to advance a new PrEP product
 - Tissue sub-study included colorectal tissue biopsies from a sample of men who have sex with men (MSM) & cisgender women (CGW)

Study objective

Compare CGW to MSM for mucosal tissue differences in pharmacokinetics, HIV infectivity and cell phenotype.

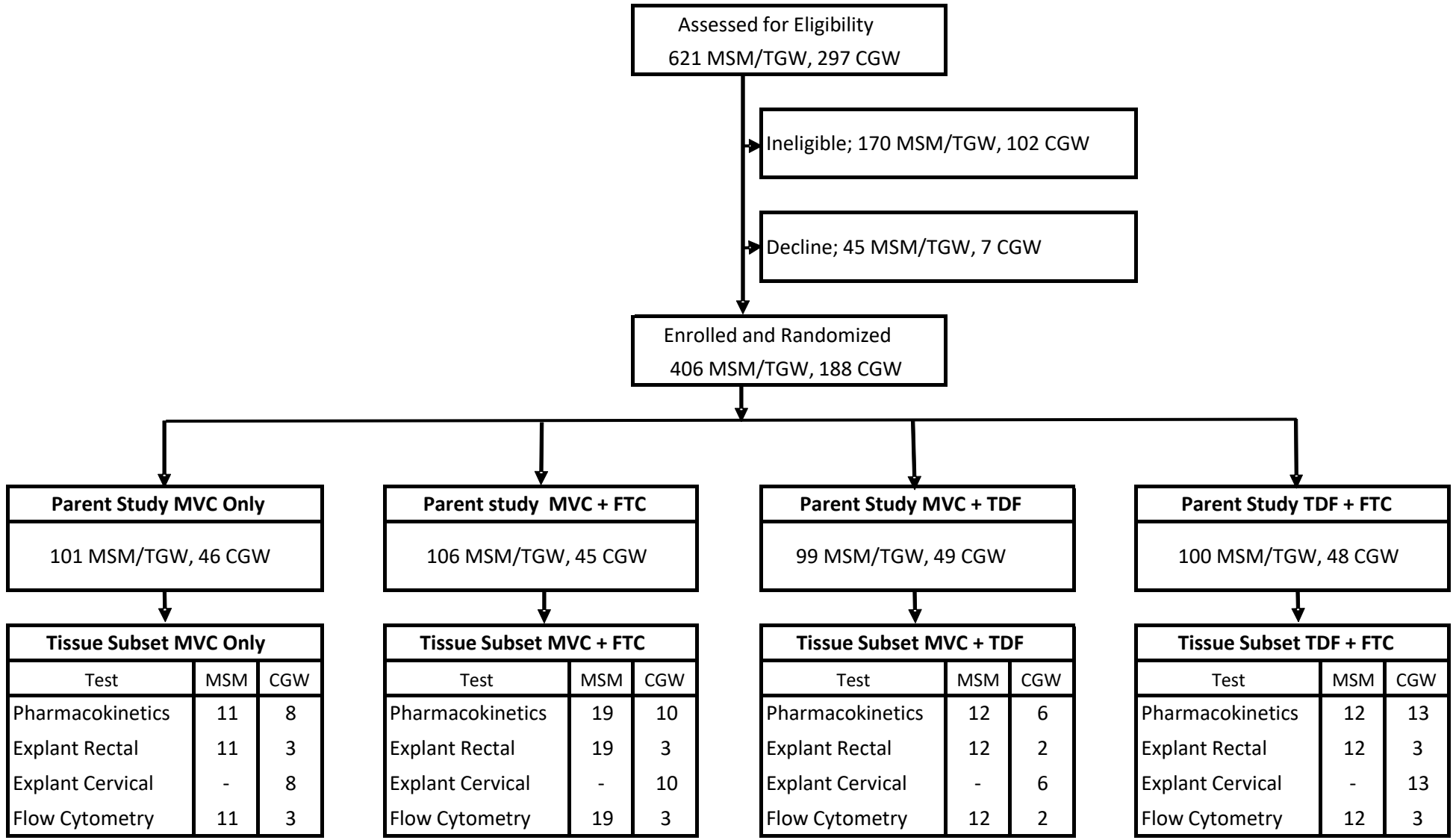
Methods

- Enroll HPTN 069 participants into tissue sub-study
 - Only MSM & CGW enrolled; no TGW
- Sample blood & colon tissue at baseline (no drug), week 24 & 48 (on ARVs), & week 49 (one week after last dose).
- Assess colon tissue “explant” HIV infectivity
 - Challenge colon biopsy “explants” with HIV ex vivo
 - Collect tissue culture supernatant over 2 weeks
 - Measure cumulative p24 antigen over 2 weeks
 - Estimate \log_{10} median (of 4 biopsies) biopsy weight-adjusted p24 antigen (pg/mL/mg) as unit of analysis

Methods

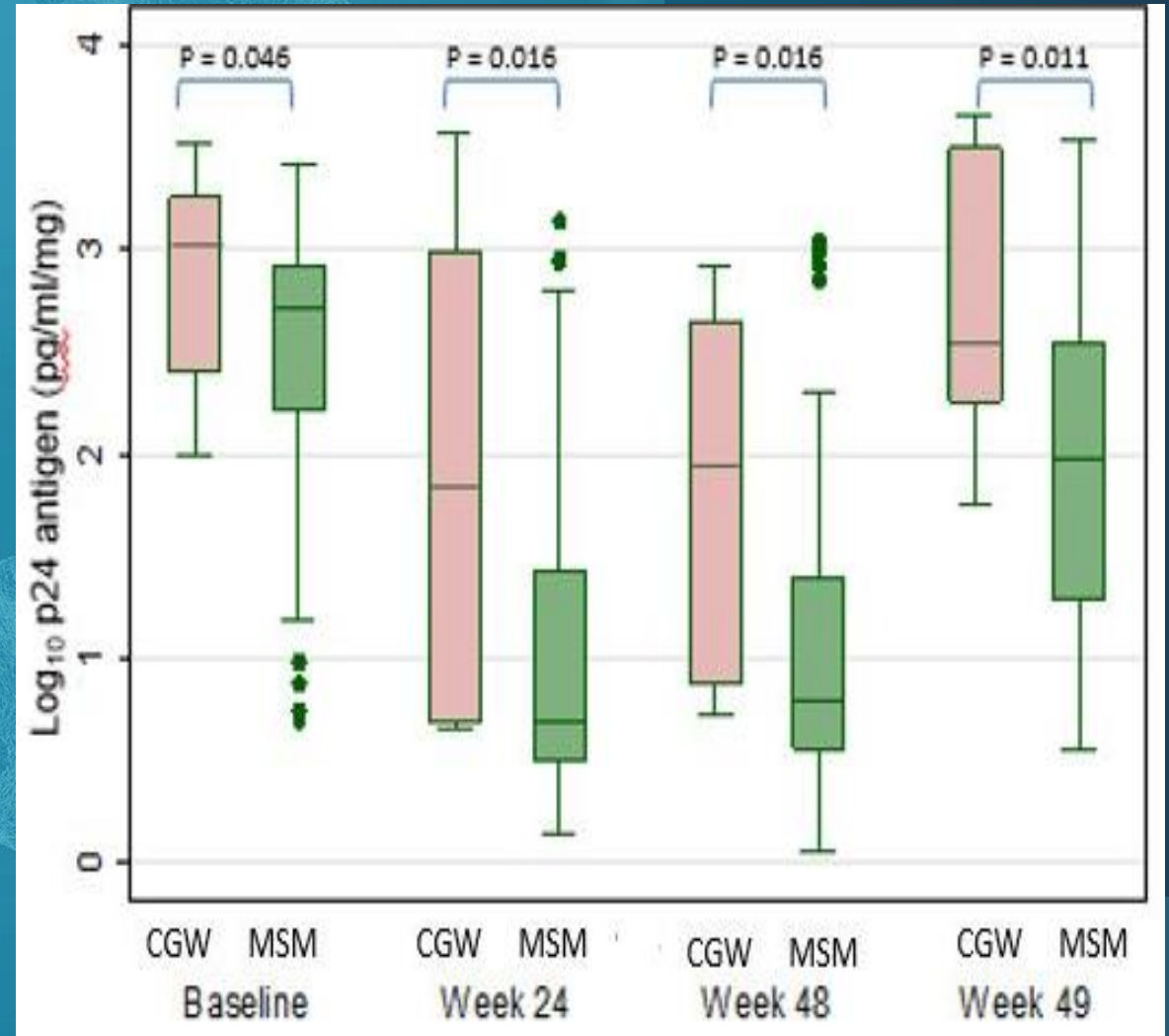
- Descriptive statistics of the laboratory measures - cell phenotype, PK, and explant (PD)
- Compare study arms across all measures
- Compare MSM to CGW using pooled data from all arms; Wilcoxon Signed Rank Test with exact significance

Sub-study Design & Evaluable Participants



Results: Log₁₀ p24 antigen by Sex & Time

- PD: CGW had higher explant p24 at all visits v. MSM
- Baseline visits (Pre-drug) 2 fold higher [p=0.046]
- Steady-state (week 24 & 48) 10-16 fold higher [p = 0.016]
- One week washout (week 49) 4 fold higher [p=0.011]



Comparison of Drug Concentrations in CGW and MSM by Matrix

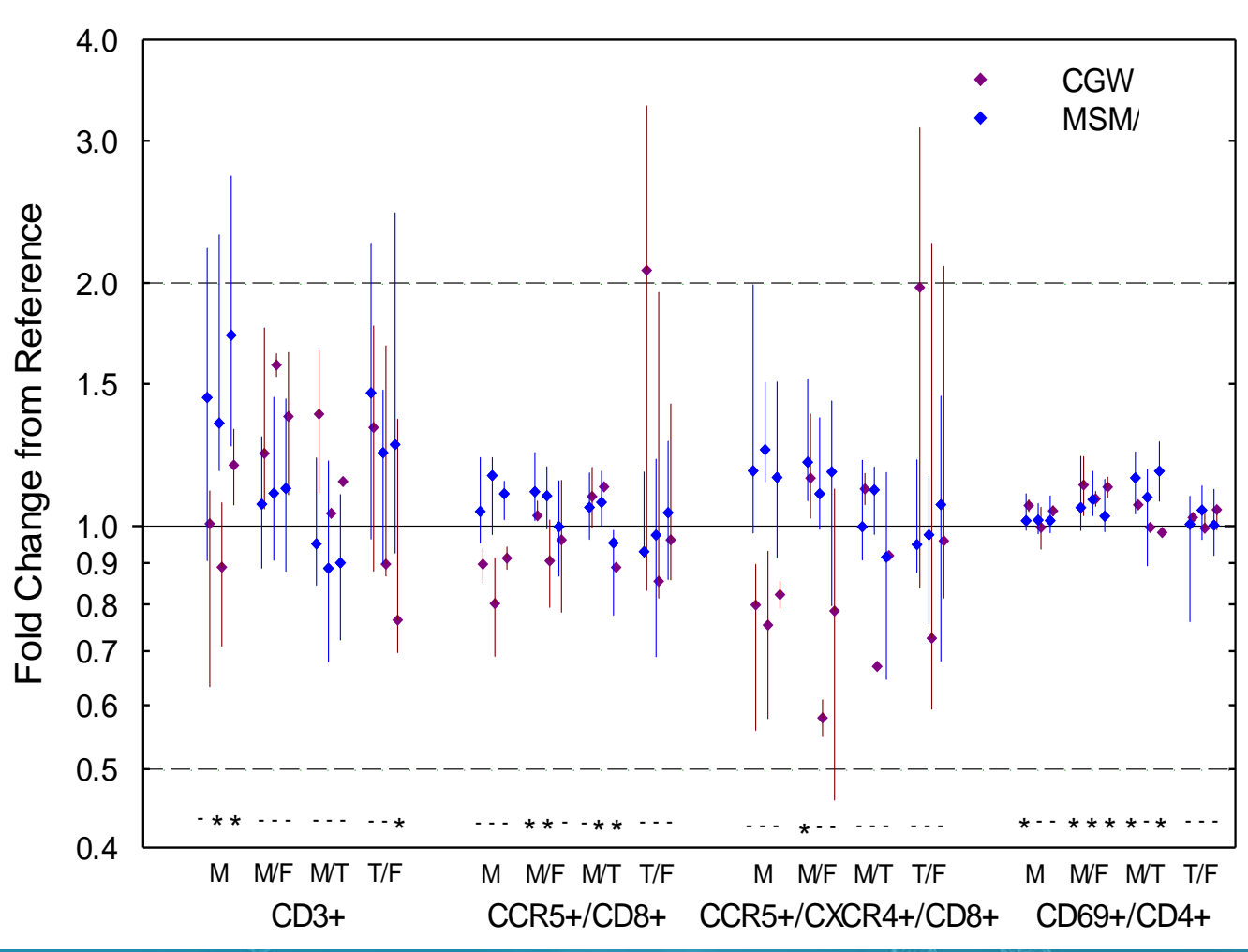
| Matrix | Analyte | Units | LLOQ | Number | | | Drug Concentration Median (IQR) | | | Below LLOQ(%) | | |
|-------------------|---------|----------------------------|-------|--------|-----|-----|---------------------------------|------------------------------|---------------------|---------------|------|------|
| | | | | Pooled | CGW | MSM | Pooled | CGW | MSM | Pooled | CGW | MSM |
| Plasma | MVC | ng/mL | 0.5 | 125 | 44 | 81 | 15.6 (6.8, 31.4) | 22.9 (10.0, 38.1)** | 13.3 (4.8, 19.9) | 8.8 | 9.1 | 8.6 |
| | TFV | ng/mL | 0.31 | 81 | 34 | 47 | 57.2 (36.0, 112.0) | 53.8 (29.3, 98.3) | 67.6 (36.0, 114.0) | 8.6 | 14.7 | 4.3 |
| | FTC | ng/mL | 0.31 | 106 | 44 | 62 | 133.5 (49.0, 346.3) | 105.5 (13.4, 333.5) | 166.5 (51.3, 376.0) | 11.3 | 18.2 | 6.5 |
| PBMC | TFV-DP | fmol/10 ⁶ cells | 0.135 | 82 | 36 | 46 | 54.5 (34.2, 93.4) | 64.0 (24.9, 117.8) | 52.3 (36.2, 82.0) | 8.5 | 13.9 | 4.3 |
| | FTC-TP | pmol/10 ⁶ cells | 5.405 | 106 | 44 | 62 | 5.7 (2.5, 8.7) | 5.4 (0.3, 9.3) | 5.7 (3.2, 8.5) | 11.3 | 18.2 | 6.5 |
| Rectal Fluid | MVC | ng/mg | 0.021 | 94 | 13 | 81 | 2.9 (0.4, 15.7) | 5.7 (0.1, 27.9) | 2.8 (0.5, 14.4) | 11.7 | 15.4 | 11.1 |
| Colorectal Tissue | MVC | ng/mg | 0.01 | 93 | 13 | 80 | 0.7 (0.2, 1.4) | 0.5 (0.1, 0.9) | 0.7 (0.3, 1.5) | 10.8 | 15.4 | 10 |
| | TFV | ng/mg | 0.003 | 54 | 8 | 46 | 1.4 (0.8, 2.1) | 1.5 (0.4, 2.0) | 1.4 (0.8, 2.1) | 5.6 | 0 | 6.5 |
| | FTC | ng/mg | 0.013 | 72 | 10 | 62 | 0.7 (0.3, 1.1) | 0.3 (0.1, 0.5)** | 0.7 (0.4, 1.1) | 9.7 | 20 | 8.1 |
| | TFV-DP | fmol/mg | 2.618 | 54 | 8 | 46 | 32.3 (19.1, 85.5) | 318.4 (89.4, 526.9)** | 26.1 (17.5, 52.7) | 7.4 | 0 | 8.7 |

Pooling Drug concentrations in Weeks 24 & 48. LLOQ = lower limit of assay quantitation. IQR = interquartile range. MVC maraviroc, TFV tenofovir, FTC emtricitabine, TFV-DP TFV diphosphate, FTC-TP FTC triphosphate. **p<0.005 based on all PK eligible participants, regardless of adherence.

Results: Adherence, PK and PD

- Sub-study included 37 CGW & 54 MSM
- Adherence (PK – defined):
 - 79% of CGW and 90% of MSM ($p < 0.05$)
- PK
 - CGW colon tissue FTC lower, only 40%, of MSM ($p = 0.004$)
 - CGW plasma MVC higher than MSM ($p < 0.005$)
 - Rectal tissue TFV-DP was significantly higher in CGW vs MSM
 - No differences observed in other matrices (PBMC, RF)
- CGW vs MSM difference (Δ):
 - $\Delta PD \gg \Delta PK > \Delta Adherence$

Cell Phenotype Comparisons



- For CD69+/CD4+ consistent difference was very small
- For other markers, inconsistent and relatively small <2 fold change
- No Important functional differences

Conclusion

- CGW in Comparison to MSM had:
 - *Greater* colon HIV replication at baseline and on ARVs
 - Varied PK colon tissue differences (\downarrow FTC, \uparrow TFV-DP)
- Adherence & PK differences only partly explain HIV infectivity differences

Future Questions

- Are these HIV infectivity differences also seen clinically?
- What is the biological mechanism of these sex differences?
- Do results warrant sex-specific PrEP dosing?

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