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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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)

- 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

Assessed for Eligibility
621 MSM/TGW, 297 CGW

Ineligible; 170 MSM/TGW, 102 CGW

Decline; 45 MSM/TGW, 7 CGW

Enrolled and Randomized
406 MSM/TGW, 188 CGW

Parent Study MVC Only
101 MSM/TGW, 46 CGW

Parent study MVC + FTC
106 MSM/TGW, 45 CGW

Parent Study MVC + TDF
99 MSM/TGW, 49 CGW

Parent Study TDF + FTC
100 MSM/TGW, 48 CGW

Tissue Subset MVC Only
Test | MSM | CGW
--- | --- | ---
Pharmacokinetics | 11 | 8
Explant Rectal | 11 | 3
Explant Cervical | - | 8
Flow Cytometry | 11 | 3

Tissue Subset MVC + FTC
Test | MSM | CGW
--- | --- | ---
Pharmacokinetics | 19 | 10
Explant Rectal | 19 | 3
Explant Cervical | - | 10
Flow Cytometry | 19 | 3

Tissue Subset MVC + TDF
Test | MSM | CGW
--- | --- | ---
Pharmacokinetics | 12 | 6
Explant Rectal | 12 | 2
Explant Cervical | - | 6
Flow Cytometry | 12 | 2

Tissue Subset TDF + FTC
Test | MSM | CGW
--- | --- | ---
Pharmacokinetics | 12 | 13
Explant Rectal | 12 | 3
Explant Cervical | - | 13
Flow Cytometry | 12 | 3
Results: $\log_{10} p24$ 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

<table>
<thead>
<tr>
<th>Matrix</th>
<th>Analyte</th>
<th>Units</th>
<th>LLOQ</th>
<th>Number</th>
<th>Drug Concentration Median (IQR)</th>
<th>Below LLOQ(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pool</td>
<td>CGW</td>
<td>MSM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pooled</td>
<td>Pooled</td>
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<td></td>
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<tr>
<td>Plasma</td>
<td>MVC</td>
<td>ng/mL</td>
<td>0.5</td>
<td>125</td>
<td>15.6 (6.8, 31.4)</td>
<td>13.3 (4.8, 19.9)</td>
</tr>
<tr>
<td></td>
<td>TFV</td>
<td>ng/mL</td>
<td>0.31</td>
<td>81</td>
<td>57.2 (36.0, 112.0)</td>
<td>53.8 (29.3, 98.3)</td>
</tr>
<tr>
<td></td>
<td>FTC</td>
<td>ng/mL</td>
<td>0.31</td>
<td>106</td>
<td>133.5 (49.0, 346.3)</td>
<td>105.5 (13.4, 333.5)</td>
</tr>
<tr>
<td>PBMC</td>
<td>TFV-DP</td>
<td>fmol/10^6 cells</td>
<td>0.135</td>
<td>82</td>
<td>54.5 (34.2, 93.4)</td>
<td>64.0 (24.9, 117.8)</td>
</tr>
<tr>
<td></td>
<td>FTC-TP</td>
<td>pmol/10^6 cells</td>
<td>5.405</td>
<td>106</td>
<td>5.7 (2.5, 8.7)</td>
<td>5.4 (0.3, 9.3)</td>
</tr>
<tr>
<td>Rectal Fluid</td>
<td>MVC</td>
<td>ng/mg</td>
<td>0.021</td>
<td>94</td>
<td>2.9 (0.4, 15.7)</td>
<td>5.7 (0.1, 27.9)</td>
</tr>
<tr>
<td>Colorectal Tissue</td>
<td>MVC</td>
<td>ng/mg</td>
<td>0.01</td>
<td>93</td>
<td>0.7 (0.2, 1.4)</td>
<td>0.5 (0.1, 0.9)</td>
</tr>
<tr>
<td></td>
<td>TFV</td>
<td>ng/mg</td>
<td>0.003</td>
<td>54</td>
<td>1.4 (0.8, 2.1)</td>
<td>1.5 (0.4, 2.0)</td>
</tr>
<tr>
<td></td>
<td>FTC</td>
<td>ng/mg</td>
<td>0.013</td>
<td>72</td>
<td>0.7 (0.3, 1.1)</td>
<td><strong>0.3 (0.1, 0.5)</strong></td>
</tr>
<tr>
<td></td>
<td>TFV-DP</td>
<td>fmol/mg</td>
<td>2.618</td>
<td>54</td>
<td>32.3 (19.1, 85.5)</td>
<td><strong>318.4 (89.4, 526.9)</strong></td>
</tr>
</tbody>
</table>

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):
  - Δ PD >> Δ PK > Δ Adherence
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 (↓FTC, ↑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?
Acknowledgments

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• HPTN 069 Protocol team and study participants

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