PrEP study reveals limited *ex vivo* potency of oral Maraviroc against HIV-1

Juan Manuel Tiraboschi¹, Carolina Herrera², Akil Jackson³, Laura Else⁴, Natalia Olejniczak², Saye Khoo⁴, David Back⁴, Robin Shattock², Marta Boffito³, Julie Fox¹

1. Guys and St. Thomas' NHS Foundation Trust, London, United Kingdom
2. Imperial College London, London, United Kingdom
3. Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom
4. University of Liverpool, Liverpool, United Kingdom
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Background

• Oral pre-exposure prophylaxis (PrEP) has a significant role in HIV prevention\textsuperscript{1,2,3}
  - Most clinical trial data relate to Tenofovir +/- FTC which act after viral entry

• Maraviroc is an attractive drug for PreP:
  - Prevents viral entry into cells
  - Rapidly absorbed in genital tract
    • rectal concentrations up to 9 x plasma concentrations after single dose\textsuperscript{1,2}
  - Safe, well tolerated
  - As such clinical trials underway notably HPTN069

\textsuperscript{1}Baeten NEJM 2012; \textsuperscript{2}Grant NEJM 2010; \textsuperscript{3}Thigpen NEJM 2012; \textsuperscript{4}Dumond JAIDS 2009; \textsuperscript{5}Brown JID 2011
**Background**

- *Ex vivo* challenge in human colorectal explants have shown maraviroc [500ng/ml] prevents 85% infections after 2hr HIV incubation\(^1\)
  - As this concentration is reached in the rectum and vagina within 2hrs of a stat 300mg oral dose \(^2,3\) it is possible that maraviroc may have a role in event driven PrEP

- Macaque data: rectal [maraviroc] >40x higher than those required to block SHIV infection in PBMCs *DO NOT* protect from rectal SHIV infection\(^4\)

- It is not known whether oral maraviroc can prevent HIV infection in humans

\(^1\)D Fletcher IAS 2009; \(^2\)Dumond JAIDS 2009 \(^3\)Brown JID 2011 \(^4\)Massud J Virol 2013
Aims

• To characterize maraviroc exposure in multiple biological compartments in men and women after a **single** oral dose of maraviroc 300mg

• To determine whether a single oral dose of Maraviroc 300mg can provide *ex vivo* protection from HIV-1

• To determine the safety and tolerability of a single oral dose of Maraviroc 300mg in HIV-1 negative individuals
Two site, open label, randomized controlled study
Healthy HIV-negative men and women: No STI at screening

HIV Negative N= 54

Control
2 sets of tissue biopsies
4 weeks apart
N=6

4 intervention arms:
300mg Maraviroc followed by tissue sampling x hours later
N=12 per arm

A
2 hours
24 hours

B
4 hours
36 hours

C
6 hours
48 hours

D
12 hours
72 hours

4 weeks washout period

A
control

B
control

C
control

D
control
Sampling post maraviroc dose

**men and women:**
- blood and rectal fluid (WEKs sponge)

**women**
- cervico-vaginal aspirate (Rovumeter)
- and vaginal biopsy

**men**
- urethral swab and a rectal biopsy

All PK samples frozen immediately at -80°C until processed.
Drug concentrations measured by LC-MS/MS.

All PD samples placed in 100ul PBS and transported immediately to Imperial College on ice: median transport time 30 mins.
Ex vivo tissue analysis

Vaginal tissue

4 washes in PBS

2 h with or without virus

Rectal tissue

Gelfoam® raft

Feeding of cultures at days 3, 7, 11 and 15
Detection of virus in supernatant (p24 ELISA)

Tissue biopsy cuts were exposed to R5-tropic HIV-1BaL
Incubated for 2h
Washed 4 times

p24 antigen levels measured in supernatants during 15 days of culture
### Baseline characteristics

<table>
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<tr>
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<th>N=54</th>
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<tbody>
<tr>
<td><strong>Age</strong></td>
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<tr>
<td>Median (range)</td>
<td>32 (20-50)</td>
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<tr>
<td><strong>Gender</strong></td>
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<tr>
<td>- Male</td>
<td>29 (55%)</td>
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<tr>
<td>- Female</td>
<td>25</td>
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<tr>
<td><strong>Ethnicity</strong></td>
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<tr>
<td>- White</td>
<td>35 (64%)</td>
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<tr>
<td>- Black African</td>
<td>15 (28%)</td>
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<tr>
<td>- Other</td>
<td>4</td>
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<tr>
<td><strong>Weight</strong></td>
<td></td>
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<tr>
<td>Mean +/- SD</td>
<td>72.74 Kg +/- 13.8</td>
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<tr>
<td><strong>BMI</strong></td>
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<tr>
<td>Mean +/- SD</td>
<td>24.5 +/- 3.60</td>
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</table>

No side effects reported from medication
Plasma, vaginal tissue and rectal tissue Cmax at 4 hours
Vaginal tissue concentration 3.6x higher than plasma at 4 hours and 26.0x higher at 72 hours
Rectal tissue concentration 9.7x higher than plasma at 4 hours and 19.0x higher at 12 hours

* Cooper JID 2010 Merit study
Correlation between plasma and vaginal tissue concentrations

Vaginal tissue and plasma $r^2 = 0.66$

Rectal tissue and plasma $r^2 = 0.39$
**Ex vivo challenge: vaginal tissue**

Reduced p24 levels at 2h (no difference from 2\textsuperscript{nd} controls)
Effect was lost by 4h post dose
Needs larger control numbers to explore further
Ex vivo challenge: rectal tissue

High levels of p24Ag at all time points
No evidence of protection
No correlation between PK/PD

Women: [plasma] vs vaginal tissue p24

Men: [plasma] vs rectal tissue p24

Women: [vaginal tissue] vs vaginal tissue p24

Men: [rectal tissue] vs rectal tissue p24

No correlation between day 15 p24 concentrations and MVC concentration in plasma, vagina or rectal tissue
Conclusion

• High maraviroc concentrations were detectable in vaginal and rectal tissue at 4h post single maraviroc dose with
  – Vaginal tissue 3.6 x plasma
  – Rectal tissue 9.7 x plasma

• No ex vivo protection or PK/PD relationship was observed in vaginal or rectal tissue after single maraviroc dose 300mg
  • PD variability is consistent with other maraviroc studies\textsuperscript{1,2}
  • Further vaginal tissue samples are being collected

• Although no protective effect of single dose maraviroc seen, this does not preclude an effect with multiple maraviroc dosing

\textsuperscript{1}Nicol JAIDS 2015; \textsuperscript{2}Massud J Virol 2013
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