The role of Raltegravir alone or combined with Lamivudine as PrEP: a phase 2 randomised controlled clinical trial

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Background

• Oral Truvada (TDF-FTC) pre-exposure prophylaxis (PrEP) is highly effective in HIV prevention\(^1,2,3\)

• Uptake varied depending on PrEP availability, cost and user engagement

• Tenofovir +/- FTC only WHO recommended regimes. Are there other options?
  – Maraviroc (CCR5 entry inhibitor) not protective\(^4\)
  – Last month elvitegravir/TAF protected macaques from rectal SIV\(^5\)

\(^1\)Baeten NEJM 2012; \(^2\)Grant NEJM 2010; \(^3\)Thigpen NEJM 2012; \(^4\) Fox JAIDS 2015; \(^5\) Doncel CROI 2019
Integrase inhibitors attractive agents for PrEP

- They lead to rapid viral suppression in HIV positive individuals
- Safe, well tolerated
- Raltegravir is the most widely used INI in UK
  - High levels found in rectal secretions suggest that it might have role in PrEP for MSM
    - Unknown whether these high levels are due to lack of absorption or persistence in tissue
3TC PrEP option

- Similar structure to FTC
- HIV treatment studies show FTC and 3TC have same efficacy
- No data in PrEP
- Some countries only use 3TC therefore Truvada is not available
- WHO difficult position: no data on 3TC PrEP but recommending it would increase availability of PrEP globally
Aims

• To describe Raltegravir and Raltegravir/3TC drug levels in multiple compartments in HIV negative men and women during and after 7-days of therapy

• To determine whether Raltegravir and/or Raltegravir/3TC can provide *ex vivo* protection from HIV-1
Design

• Open label RCT trial of 36 HIV negative females and males (1:1) randomised to 7 days PrEP:
  – either Raltegravir 400mg bd followed by a month washout and then 7d Raltegravir 400mg/3TC 150mg bd or vice versa
  – in 6 sampling blocks to capture different times on and off ART
HIV negative volunteer
Tissue biopsies to confirm no protection from HIV

Phase 1
- Raltegravir 400mg bd
  - biopsy 2
    - Day 2,8
    - Day 4, 10
    - Day 6,12

Phase 2
- Raltegravir 400mg /3TC 150mg bd
  - biopsy 4
    - Day 2,8
    - Day 4, 10
    - Day 6,12

Raltegravir 300mg /3TC 150mg bd
  - Day 2,8
  - Day 4, 10
  - Day 6,12

Raltegravir 400mg bd
  - Day 2,8
  - Day 4, 10
  - Day 6,12
**Samples**

**Men and women:**
- Blood
- Oral fluid
- Urine
- Rectal fluid (WEKs sponge)
- Rectal tissue biopsies (for PD and PK)

**Women also had:**
- Vaginal fluid
- Vaginal tissue biopsies (for PD and PK)

First time rectal samples been taken from women for PD analysis
**Ex vivo tissue analysis**

- **Vaginal tissue**
- **Rectal tissue**
- **Gelfoam® raft**

**Procedure:**
- 4 washes in PBS
- Feed cultures at days 3, 7, 11, and 15
- 2 h with or without virus R5-tropic HIV-1BaL

**Results:**
- p24 antigen levels measured in supernatants during 15 days of culture (p24 ELISA)

**Protection:**
- Defined as >60% reduction in p24 compared to baseline at day 15
## Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=36</th>
</tr>
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<tbody>
<tr>
<td><strong>Age</strong></td>
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</tr>
<tr>
<td>Median (range)</td>
<td>32 (20-50)</td>
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<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>- Male</td>
<td>18</td>
</tr>
<tr>
<td>- Female</td>
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<tr>
<td><strong>Ethnicity</strong></td>
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<tr>
<td>- White</td>
<td>23 (64%)</td>
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<tr>
<td>- Black African</td>
<td>11 (30%)</td>
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<tr>
<td>- Other</td>
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</tbody>
</table>

No side effects reported from medication
Women tolerated rectal biopsies extremely well
Plasma, vaginal tissue and rectal fluid PK

Raltegravir levels:
- Very high levels seen in rectum which persist after stopping ART- in tissue not stool
- Plasma and vaginal levels lower and correlate (p=0.0071)

3TC levels:
- Highest in rectum. But vaginal levels higher than with Raltegravir and remain high after stopping ART
Ex vivo protection from HIV-1

Raltegravir alone:
- 70-80% protection achieved by day 2. Similar protection in vagina and rectum.
- Protection reducing after day 10

Raltegravir/3TC:
- Rectum: 100% protection from day 2 until day 8 then down to 80% thereafter
- Vagina: 65% protection day 2. increasing to 100% protection at day 8
- ?added value of 3TC
Relationship between drug level and protection

Vaginal Raltegravir

- $r^2 = 0.06$
- $P = \text{ns}$

Rectal: Raltegravir

- $r^2 = 0.08$
- $P = 0.0012$

Vaginal: 3TC

- $r^2 = 0.08$
- $P = \text{ns}$

Rectal: 3TC

- $r^2 = 0.09$
- $P = 0.0148$

Why?
Other results

• No gender difference between men and women found for PK or PD in rectal tissue
  – Future PK/PD studies can be women only

• Await:
  – tissue and oral drug levels
Conclusion

• Raltegravir and Raltegravir/3TC PrEP was well tolerated
• Rapid protection was observed in both arms with addition of 3TC leading to greater protection in rectum and longer and greater protection in vaginal tissue
• These data support further investigation of these agents for PrEP
  – Possible indication: individuals intolerant of Truvada
• 3TC data provides more evidence for its use as a FTC PrEP alternative
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