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

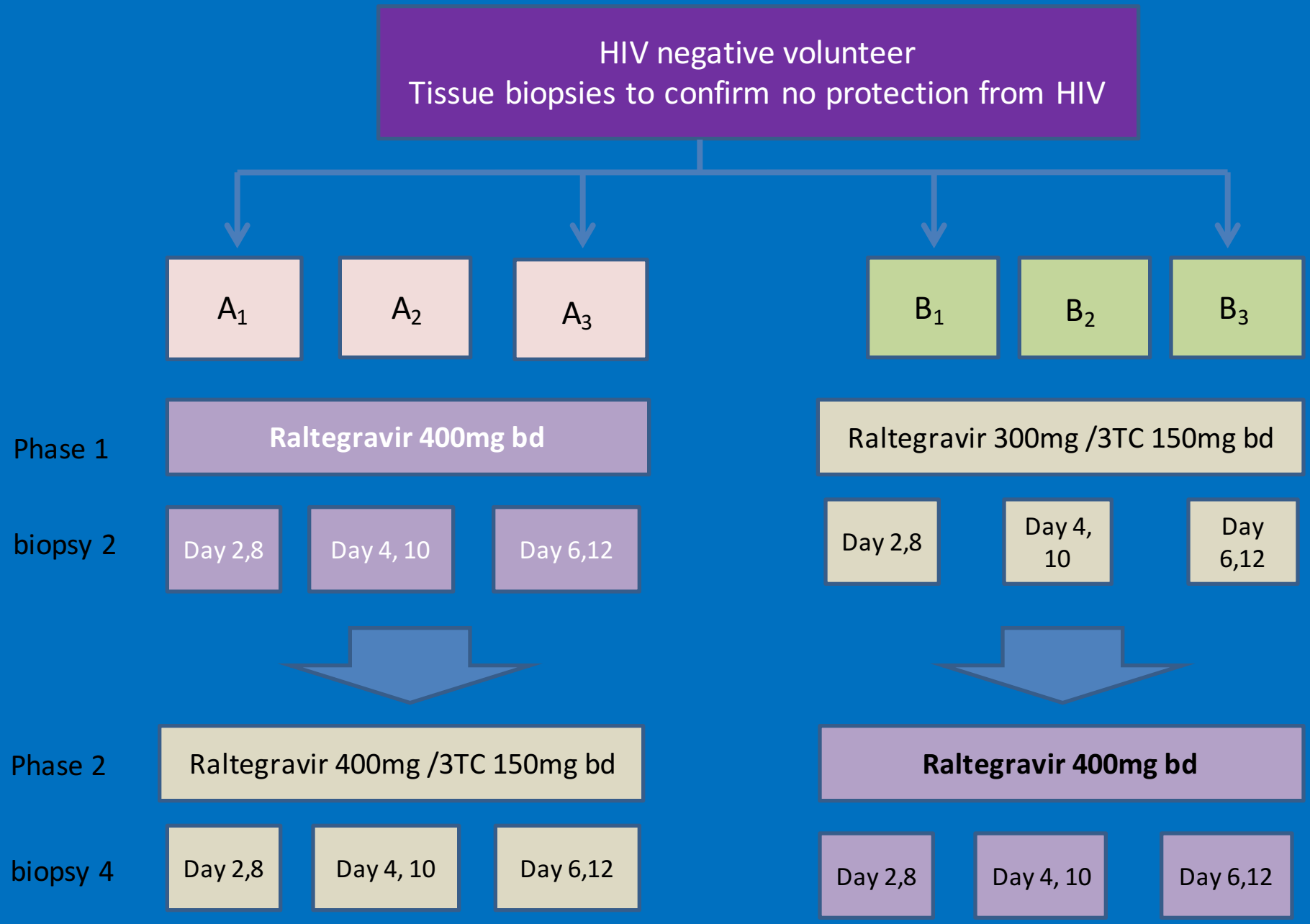
Aims

- 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 7days 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
A1
A2
A3
B1
B2
B3
Phase 1
Raltegravir 400mg bd
Raltegravir 300mg /3TC 150mg bd
biopsy 2
Day 2,8
Day 4, 10
Day 6,12
Day 2,8
Day 4, 10
Day 6,12
Phase 2
Raltegravir 400mg /3TC 150mg bd
Raltegravir 400mg bd
biopsy 4
Day 2,8
Day 4, 10
Day 6,12
Day 2,8
Day 4, 10
Day 6,12

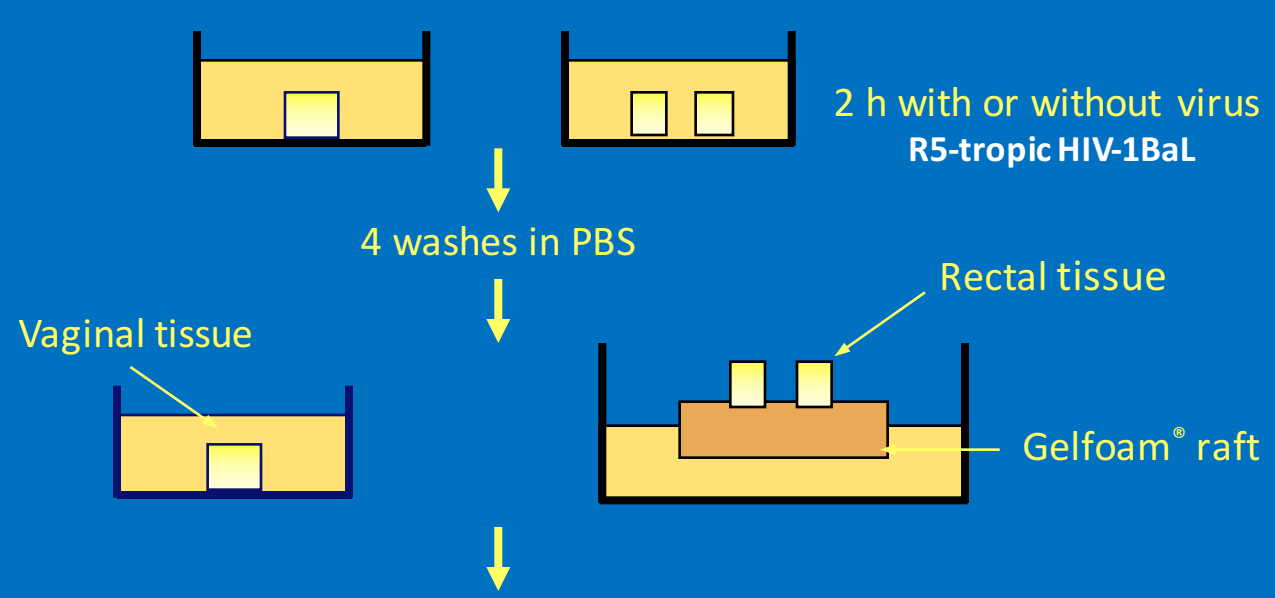
Samples

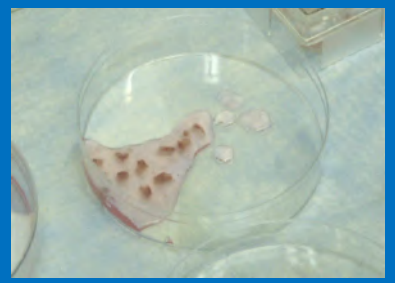
Men and women:
Blood
Oral fluid
Urine
Rectal fluid (WEKs sponge)
Rectal tissue biopsies (for PD and PK)

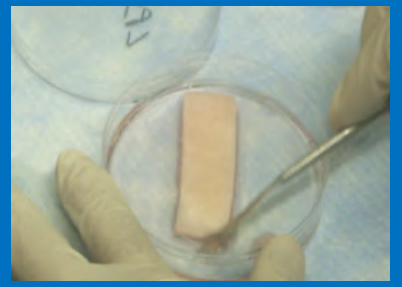
Women also had:
Vaginal fluid
Vaginal tissue biopsies (for PD and PK)

First time rectal samples been taken from women for PD analysis

Ex vivo tissue analysis







Protection defined as >60% reduction in p24 compared to baseline at day 15

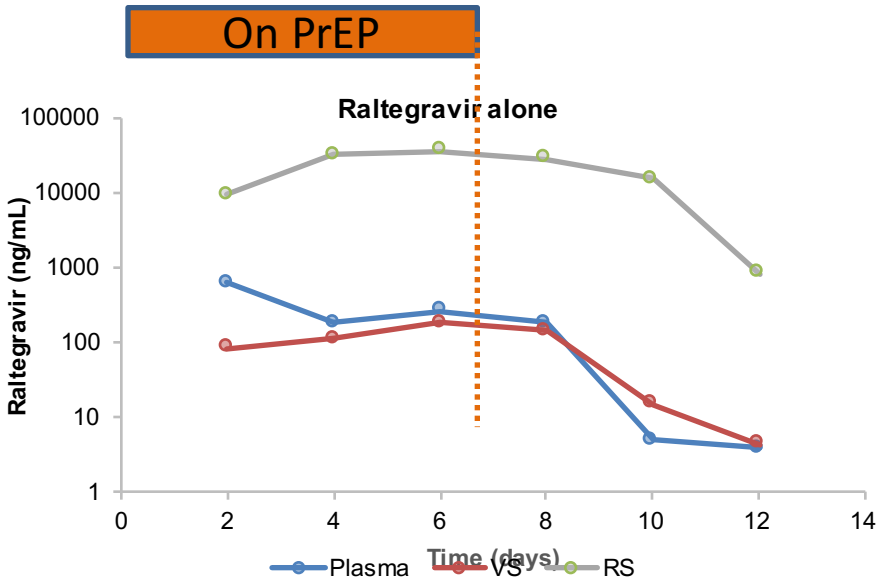
Baseline characteristics

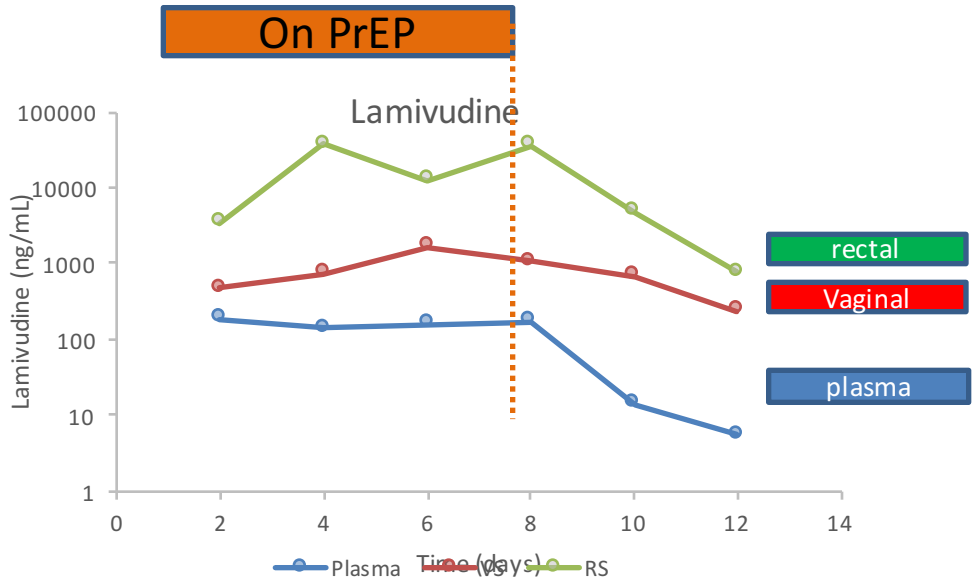
	N=36
Age Median (range)	 32 (20-50)
Gender - Male - Female	 18 18
Ethnicity - White - Black African - Other	 23 (64%) 11(30%) 2

No side effects reported from medication

Women tolerated rectal biopsies extremely well

Plasma, vaginal tissue and rectal fluid PK





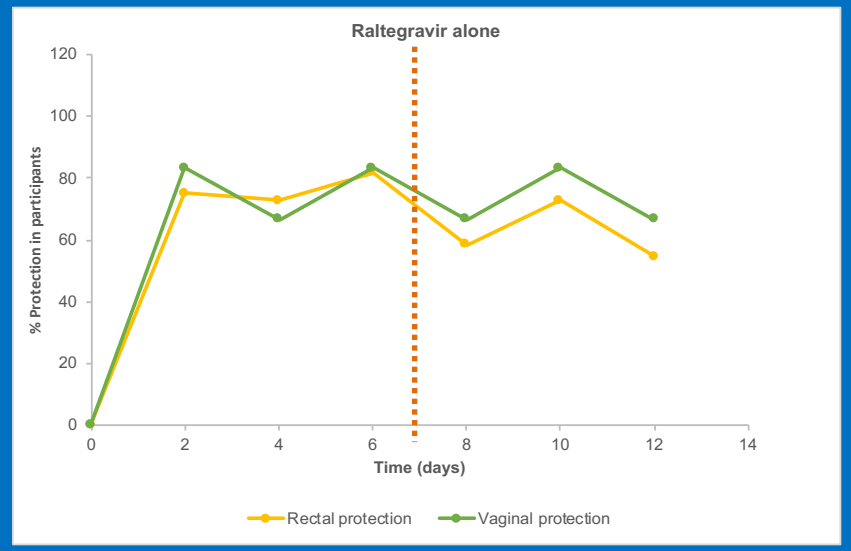
Raltegravir levels:

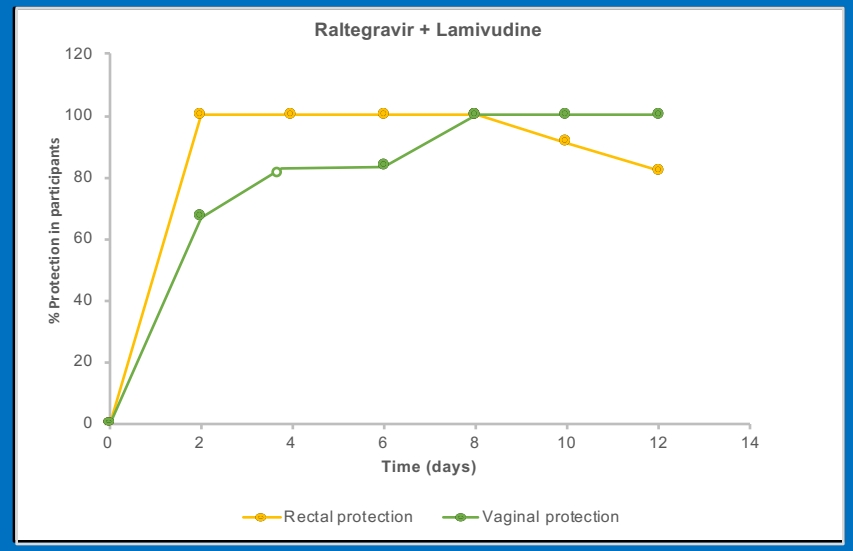
- Very high levels seen in rectum which persist after stopping ART- in tissue not stool
- Plasma and vaginal levels lower and correlate (p=0.0071)

3TC levels:

- Highest in rectum. But vaginal levels higher than with Raltegravir and remain high after stopping ART

Ex vivo protection from HIV-1



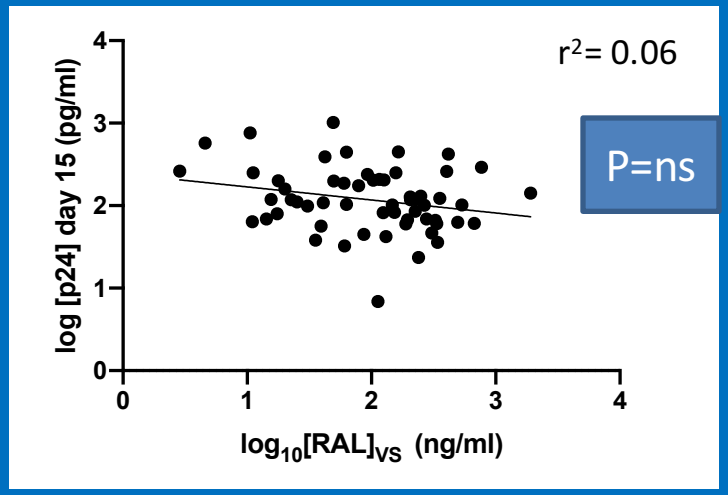


Raltegravir alone:
- 70-80% protection achieved by day 2. Similar protection in vagina and rectum. Protection reducing after day 10

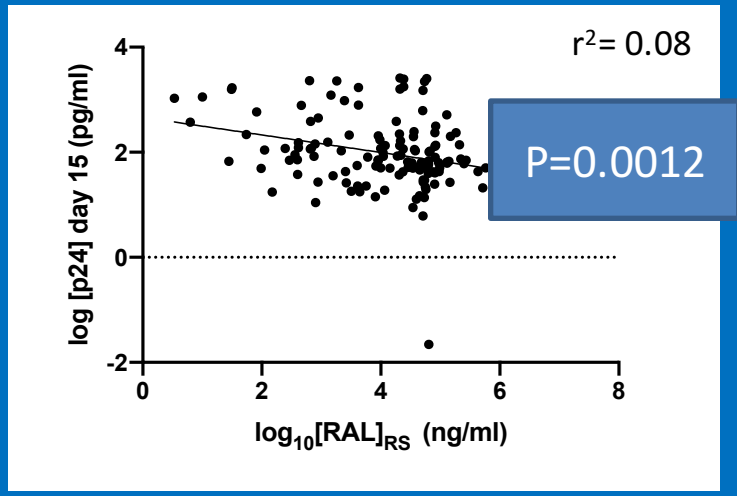
Raltegravir/3TC:
- Rectum: 100% protection from day 2 until day 8 then down to 80% thereafter
- Vagina: 65% protection day 2. increasing to 100% protection at day 8
- ?added value of 3TC

Relationship between drug level and protection

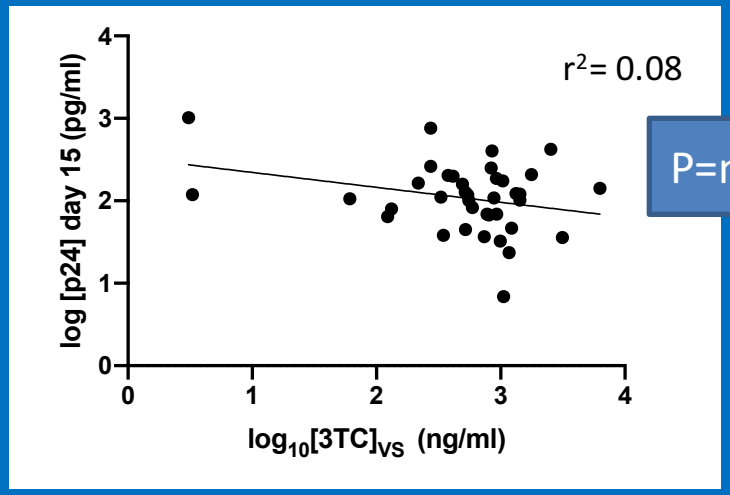
Vaginal Raltegravir



Rectal: Raltegravir

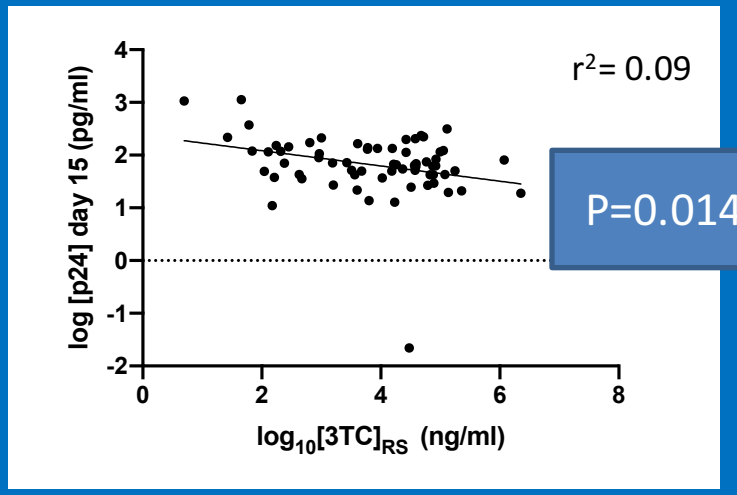


Vaginal: 3TC



Why?

Rectal: 3TC



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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