CLINICAL STUDY REPORT

R-PrEP

The time to protection and adherence requirements of Raltegravir with or without lamivudine in protection from HIV infection

Sponsor Protocol Code:	JF-007
EudraCT Number:	2016-000437-43
ClinicalTrials.gov Identifier:	NCT03205566
REC Number:	17/LO/0094
Investigational Drugs (IMPs):	Raltegravir, Lamivudine
Indication:	HIV
Development Phase:	IV
Study Begin (FPFV):	23/07/17
Study End (LPLV):	24/09/18
Report Version & Issue Date:	V1.0 05/12/19
Co-sponsor Name and Address:	N/A
Co-sponsor contact details:	N/A
Chief Investigator:	Dr Julie Fox

SIGNATURE PAGE

By signing below I approve the contents of this Clinical Study Report, and confirm that to the best of my knowledge it accurately describes the conduct and results of the study. The clinical trial reported herein was conducted in accordance with the principles contained in the Declaration of Helsinki, Good Clinical Practice (GCP) and all applicable laws and regulations.

Chief Investigator:

Printed name: Dr Julie Fox **Signature**  **Date: 06/12/19**

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APPENDICES

1. Ethics

Independent Ethics Committee or Institutional Review Board
The study protocol and amendments were reviewed and approved by a National Research Ethics Service -NRES Committee London-Surrey Borders.

Ethical conduct of the study
The trial was conducted according to the protocol and in compliance with the principles of the Declaration of Helsinki (1996) as amended, the principles of Good Clinical Practice (GCP) and in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, the Research Governance Framework for Health and Social Care, the Data Protection Act 1998 and other regulatory requirements as appropriate. The trial protocol and substantial amendments were reviewed by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA).

Subject information and consent

Potential participants were identified via a number of methods, including study poster, internal recruitment emails within recruiting institutions, and via a list of previous HIV negative individuals who had participated in trials and who had consented to be contacted for further research. Once potential participants contacted the trial team, the trial was discussed with them and if still interested, a participant information sheet was sent to them. If they still wished to proceed, a screening visit was booked for them and written informed consent was obtained.

2. Data Monitoring

There was no data monitoring committee for this study. However the sponsor and investigators mett on a regular basis to review recruitment and safety.

3. Sponsors, Investigators and Trial Sites

5. Study Synopsis

Title of clinical trial	The time to protection and adherence requirements of Raltegravir with or without lamivudine in protection from HIV infection
Protocol Short Title/Acronym	**R-PrEP**
Study Phase	**IV**
Sponsor name	**Guy's & St. Thomas' NHS Foundation Trust**
Chief Investigator	**Dr Julie Fox**
Eudract number	016-000437-43
REC number	17/LO/0094
IRAS project ID:	202316
Medical condition or disease under investigation	**HIV**
Purpose of clinical trial	To investigate the role of Raltegravir +/- lamivudine in HIV prevention
Primary objective	To determine the level of drug (raltegravir & laminudine) required in the plasma, vagina and rectum for mucosal *ex vivo* protection from HIV
Secondary objective (s)	• To determine the time from first dose of drug to mucosal *ex vivo* protection from HIV infection • To determine the time to cessation of mucosal *ex vivo* protection from HIV after stopping ART at steady state. • To determine the safety and tolerability of Raltegravir based PreP in HIV negative individuals
Trial Design	Phase IV, open-label, randomised controlled trial (RCT)
Endpoints	**Primary:** The level of Raltegravir alone or Raltegravir /lamivudine required in the plasma, vagina and rectum for 100% *ex vivo* protection from HIV **Secondary** 1. The time from first dose of drug to mucosal *ex vivo* protection from HIV infection 2. The time to cessation of mucosal *ex vivo* protection from HIV after stopping ART at steady state. 3. The safety and tolerability of Raltegravir

	based PrEP in HIV negative individuals
Planned number of subjects	36
Summary of eligibility criteria	**Inclusion Criteria** 1. The ability to understand and sign a written informed consent form prior to participation in any screening procedures and must be willing to comply with all trial requirements. 2. Male or non-pregnant, non-lactating females 3. Age between 18 to 60 years, inclusive. 4. Body Mass Index (BMI) of 16 to 35 kg/m2, inclusive. 5. Negative antibody/antigen combined test for HIV. 6. Absence of any significant health problems (in the opinion of the investigator) on the basis of the screening procedures; including medical history, physical examination, vital signs. 7. Women participating in sexual intercourse that could result in pregnancy must use an adequate form of contraception throughout the study and for two weeks after the study. This includes intrauterine device, condoms, anatomical sterility in self or partner. Oral hormonal methods and implant contraceptives are allowed but only in combination with the additional protection of a barrier method. 8. Female participants may not use any vaginal products or objects or have vaginal sex for 48 hours before and after the collection of vaginal fluid and vaginal biopsies. This list includes tampons, female condoms, cotton wool, rags, diaphragms, cervical caps (or any other vaginal barrier method),douches, lubricants, vibrators/dildos, and drying agents. 9. Males participating in sexual intercourse that could result in pregnancy must use condoms during the duration of the study. 10. Men and women cannot use anal products or objects including but not exclusive to douches, lubricants and vibrators/dildos, butt plugs or urethral sounds or have receptive anal intercourse for 48 hours before and after the collection of rectal biopsies. 11. Willing to abstain from St. John's Wort, multivitamins and antacids for the study duration. **Exclusion Criteria** 1. Any significant acute or chronic medical

	illness as determined by the investigator. 2. Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs or clinical laboratory determinations. 3. Positive blood screen for hepatitis B (HBs Ag) and/or C antibodies. 4. Positive blood screen for HIV antibody/antigen by 4th generation assay. 5. Positive screen for sexually transmitted infections at screening visit 6. High-risk behaviour for HIV infection, which is defined as having one of the following within three months before trial day 0 (first dose): i. had unprotected vaginal or anal sex with a known HIV infected person or a casual partner. ii. engaged in sex work for money or drugs. iii. acquired a bacterial sexually transmitted disease. iv. having a known HIV positive partner either currently or in the previous six months 7. Females who are pregnant or breast-feeding. 8. Clinically significant laboratory abnormalities 9. Ingestion of H2 receptor antagonists or proton pump inhibitor drugs in the preceding 14 days 10. Current of planned use of anti-epileptics
IMP, dosage and route of administration	Oral Raltegravir 400mg bd alone or Raltegravir 400mg/lamivudine 150mg bd for 7 days
Active comparator product(s)	Raltegravir, Lamivudine
Maximum duration of treatment of a subject	7 days Raltegravir 400mg bd followed by 4 weeks wash out and then 7 days Raltegravir 400mg/lamivudine 150mg (oral tablets) bd. Or vice versa.
Version and date of protocol amendments	**V1.3 08/08/18**

6. Glossary of terms

AE – adverse event
AIDS - acquired immunodeficiency syndrome
ART – antiretroviral therapy
BMI – body mass index
CNST – clinical negligence scheme for trusts
CRF – case report/record form
CVF – cervico-vaginal fluid
DSUR – development safety update report
EDTA - ethylenediaminetetraacetic acid
FBC – full blood count
FDA – US food & drug administration
GCP – good clinical practice
Hb - haemoglobin
HIV - human immunodeficiency virus
IMP – investigational medicinal product
KCL – King's College London
KHP CTO – King's Health Partners Clinical Trials Office
LFTs – liver function tests
MHRA – medicines & healthcare products regulatory agency
MSM – men who have sex with men
PBMC – peripheral blood mononuclear cell
PD – pharmacodynamics
PK – pharmacokinetics
PrEP – pre-exposure prophylaxis
RCT – randomised controlled trial
REC – research ethics committee
SAE – serious adverse event
SAR – serious adverse reaction
SmPC – summary of product characteristics
SOP – standard operating procedure
SUSAR – suspected unexpected serious adverse reaction

7. Publication (reference)

Include all references to any publications.

8. Study period (years)

The first patient visit (FPFV) was on 19th September 2017 and the last patient last visit (LPLV) was on 27th September 2018. The last patient was recruited on 14th June 2018. There were no study interruptions (temporary halts) and the trial was not terminated prematurely.

9. Phase of development

IV

10. Objectives

For each regimen – (TRUVADA® versus DESCOVY®) we have the following aims:

Part 1:

To determine the level of drug required in the plasma, saliva, vagina and rectum for ex *vivo* protection from HIV-1

Part 2:

To determine the minimal dosing requirement for on demand PrEP

11. Background and Context

Pre-exposure prophylaxis (PrEP) is a rapidly emerging prevention strategy that could help reduce HIV incidence globally (iPrEx, Grant 2010; Partners PrEP, Baeten 2012; TDF2, Thigpen 2012; FEM-PrEP Van Damme 2012). The use of daily oral Truvada for PrEP has demonstrated efficacy and is licenced in the USA (FDA 2012).

Raltegravir is promising as a PrEP agent, particularly for men who have sex with men- It is well tolerated, has few drug-drug interactions and has good penetration into rectal tissue- plateau levels are 1.5-7x higher in gut associated lymphoid tissue compared to plasma (Patterson PK Workshop 2012). However, it is not known whether tissue penetration is equal between men and women or whether Raltegravir on its own or in combination with lamivudine can provide *ex vivo* protection from HIV.

Raltegravir may provide tissue penetration through absorption into the circulation. In addition there are 2 further ways in which Raltegravir may access the rectum: firstly, directly as unabsorbed drug carried in faeces or secondly that it is excreted in a conjugated form by the bile duct and de-conjugates in the large bowel back to Raltegravir.

The efficacy of Raltegravir in the female genital tract and in the rectum can be evaluated by ex vivo challenge of mucosal tissue explants. This model has become essential for microbicide pre-clinical evaluation (Herrera 2014), for measurement of drug combination activity (Herrera 2009, Herrera 2011) and for HIV transmission studies (Shaw 2012). Importantly, several

studies have shown its capacity to evaluate in vivo efficacy not only in non-human primates (Cranage et al. 2008, Wallace et al.2009, Ouattara et al. 2014) but also in clinical trials (Richardson-Harman et al. 2012), and is currently used as a routine technique in microbicide trials performed by the Microbicide Trial Network. Despite the variety of models, it has been shown that consistent results can be obtained among different laboratories through protocol standardization (Richardson-Harman et al. 2009). The ex vivo challenge approach is currently being used to assess efficacy, proof of concept and insight into adherence requirements for other oral PrEP agents (HPTN069 and UK PrEP group). The information collected provides milestone data before embarking on large scale efficacy studies, informs on the possibility of event driven versus daily PrEP and can provide useful licensing data should efficacy be shown.

A number of key issues in the use of Raltegravir for PrEP are unknown:

1. The concentration of Raltegravir in either plasma or genital tract required for 100% *ex vivo* protection from HIV in PrEP
2. The pharmacokinetic (PK) profile of different Raltegravir containing regimens given orally in HIV negative individuals both in the plasma and genital tract (vagina, rectum)
3. The frequency of Raltegravir dosing required for *ex vivo* protection from HIV
4. The correlation between plasma and genital tract Raltegravir drug levels and *ex vivo* protection from HIV infection

This study evaluates whether a 7-day course of Raltegravir 400mg bd or Raltegravir 400mg/lamivudine 150mg bd can prevent HIV from infecting genital tissue and will relate the level of drug in the blood to the level of drug in genital tissue and to the ability to of HIV to infect genital tissue. As well as determining whether these regimes can provide *ex vivo* protection against HIV, this study will also determine speed to provision of protection and a 48 hour PK/PD decay profile of Raltegravir following drug cessation after attaining steady state concentrations. The results will also inform all future HIV pre-exposure prophylaxis studies of Raltegravir and form the basis for large scale clinical trials without the need for tissue sampling. To date, efficacy studies assessing PrEP regimens have utilized HIV-acquisition endpoints with the consequence being such studies are required to be large in subject number in order to power observations. In addition the study will provide for the first time data on HIV protection rather than just Raltegravir drug levels in tissue, and allow assessment of the possibility of Raltegravir being used as an intermittent dosing regimen in PrEP.

By recruiting men and women, data on plasma pharmacokinetics and the relative distribution kinetics in the female genital tract and male rectal compartment will be generated which will support expanded safety studies and a large global efficacy trial. This pharmacodynamic model is the optimal and only practical way to address the clinical question of duration of protection given the uncertainty regarding the time of transmission under real-life conditions. As each phase will be scheduled to avoid menstruation and sampling of women will occur at similar stages of the menstrual cycle.

12. Methodology

Headings below are suggestions only and can be deleted if not applicable

This is a multi-site, open-label, randomised, pharmacokinetic (PK) and pharmacodynamic (PD) trial whereby 36 individuals (18 women and 18 men) will be randomised according to gender 1:1:1:1:1:1 to one of 6 arms (A_1 A_2 A_3 B_1 B_2 B_3). The result being 3 women and 3 men will be in each arm. The letter dictates the ART regimen order and the number dictates the time points that tissue sampling will occur on and off ART.

Regimes

Two ART regimes will be investigated and all individuals will receive both regimes separated by a minimum of 4 week wash out.

- Arm A (A_1 A_2 A_3): will start with 7 days Raltegravir 400mg bd and then have a minimum 4 week wash out before then starting 7 days Raltegravir 400mg /lamivudine 150mg bd.
- Arm B (B_1 B_2 B_3): will start with 7 days Raltegravir 400mg /lamivudine 150mg bd and then have a minimum 4 week wash out before then starting 7 days Raltegravir 400mg bd. This will remove sequential selection bias.

For each phase (part 1 & 2):

A_1 & B_1 will have sampling visits on day 2 and 8 post first dose

A_2 & B_2 will have sampling visits on day 4 and 10 post first dose

A_3 & B_3 will have sampling visits on day 6 and 12 post first dose

All individuals will receive tissue sampling at baseline for *ex vivo* analysis to ensure biopsies are infectable on challenge assays. Sampling from women will avoid menstruation and if possible focus on the luteal phase of the menstrual cycle. Individuals will receive another set of tissue sampling during and after ART in phase 1, have a minimum 4 week wash out period and then have another set of sampling during and after ART in phase 2. Individuals will therefore have 5 sets of sampling during the trial.

Trial Duration : 13 months

Trial Medication

Raltegravir (Isentress®)400 mg tablets in a 60 tablet pack.
Lamivudine 150mg film-coated tablets, 60 tablet, blister pack

Dosing Regimen

Raltegravir 400mg tablet bd for 7 days
Raltegravir 400mg + lamivudine 150mg bd for 7 days

Both regimes are taken twice a day. Participants will be advised to take tablets at 11am and 11pm.

Trial Visit Schedule

Day	Screen	0														
visit number	1	2	3	3	3	4	4	4		5	6	6	6	7	7	7	8
		on ART					Off ART			on ART					off ART		
Eligibility	x																
Informed consent	x																
Demographics	x																
Medical History	x																
HIV test & Syphillis RPR	x																
Randomisation		x							WASH OUT PERIOD								
IMP Dispensing		x								x							
Directed physical exam	x	x	one time point			one time point				x	one time point			one time point			x
Asymptomatic STI screen	x																
-Hep C Ab	x																
-HepBsAg	x																
FBC, U&E, ALT	x																
drug levels (vaginal/rectal/oral)			one time point			one time point					one time point			one time point			
Plasma Drug levels (PK)*			one time point			one time point					one time point			one time point			
Rectal/vaginal biopsy (PK/PD)		X***	one time point			one time point					one time point			one time point			
Pregnancy Test	x	X								X				x			
progesterone (women only)		x	one time point			one time point					one time point			one time point			
Conmed Reporting	x	x	x			x				x	x			x			x
Adverse Event Reporting		x	x			x				x	x			x			x

13. Number of patients (planned and analysed)

13.1 Planned

The planned sample size for the study was 36 participants.

13.2 Analysed

A total of 45 individuals were screened for the study. Seven participants withdrew or were not eligible to participate in the study prior to receipt of any study drug.

One participant attended all visits, but was retrospectively withdrawn from the study. This participant was subsequently found have a HIV positive sexual partner and so did not meet the study entry criteria. One individual withdrew at Visit 4 for inability to provide a vaginal sample due to menstruation. As the latter two participants did receive study drug, they were excluded from the efficacy analyses, but were included in the listings for adverse events

Table: The reasons for patient withdrawal from the study

Patient	Comments
4	Screened but not eligible – high ALT values
6	Retrospectively excluded as has HIV positive sexual partner. As received study drug, included in adverse event analysis
7	Withdrew prior to randomisation – adherence concern
22	Withdrew prior to randomisation – adherence concern
25	Withdrew prior to randomisation – adherence concern
31	Withdrew prior to randomisation – withdrew consent
35	Screened but not eligible – sexually transmitted infection
37	Retrospectively excluded at Visit 4 as unable to provide vaginal sample As received study drug, included in adverse event analysis
40	Screened but not randomised as missed baseline study visit

14. Diagnosis and main criteria for inclusion

1. The ability to understand and sign a written informed consent form prior to participation in any screening procedures and must be willing to comply with all trial requirements.
2. Male or non-pregnant, non-lactating females
3. Age between 18 to 60 years, inclusive.
4. Body Mass Index (BMI) of 16 to 35 kg/m2, inclusive.
5. Negative antibody/antigen combined test for HIV.
6. Absence of any significant health problems (in the opinion of the investigator) on the basis of the screening procedures; including medical history, physical examination, vital signs.
7. Women participating in sexual intercourse that could result in pregnancy -must use an adequate form of contraception throughout the study and for two weeks after the study. This includes intrauterine device, condoms, anatomical sterility in self or partner. Oral hormonal methods and implant contraceptives are allowed but only in combination with the additional protection of a barrier method.
8. Female participants may not use any vaginal products or objects or have vaginal sex for 48 hours before and after the collection of vaginal fluid and vaginal biopsies. This list includes tampons, female condoms, cotton wool, rags, diaphragms, cervical caps (or any other vaginal barrier method),douches, lubricants, vibrators/dildos, and drying agents.
9. Males participating in sexual intercourse that could result in pregnancy must use condoms during the duration of the study.
10. Men and women cannot use anal products or objects including but not exclusive to douches, lubricants and vibrators/dildos, butt plugs or urethral sounds or have receptive anal intercourse for 48 hours before and after the collection of rectal biopsies.
11. Willing to abstain from multivitamins and antacids for the study duration.

15. Test product, dose and mode of administration

IMP : Raltegravir 400mg tablet bd for 7 days, then Raltegravir 400mg + lamivudine 150mg bd for 7 days, or vice versa

16. Duration of treatment

7 days of each regimen with a one month wash out period between.

17. Reference therapy, dose and mode of administration

Raltegravir 400mg tablet bd for 7 days, then Raltegravir 400mg + lamivudine 150mg bd for 7 days, or vice versa

18. Criteria for evaluation: Endpoints

Primary endpoints

The level of Raltegravir alone or Raltegravir /lamivudine required in the plasma, vagina and rectum for 100% *ex vivo* protection from HIV

Secondary endpoints

1. The time from first dose of drug to mucosal *ex vivo* protection from HIV infection
2. The time to cessation of mucosal *ex vivo* protection from HIV after stopping ART at steady state.
3. The safety and tolerability of Raltegravir based PrEP in HIV negative individuals

18.1 Efficacy

Primary Efficacy Parameters

The level of Raltegravir alone or Raltegravir /lamivudine required in the plasma, vagina and rectum for 100% *ex vivo* protection from HIV.

Secondary Efficacy Parameters

1. Time from first dose of drug to mucosal *ex vivo* protection from HIV infection
2. Time to cessation of mucosal *ex vivo* protection from HIV after stopping ART at steady state
3. Safety and tolerability of Raltegravir based PreP in HIV negative individuals

18.2 Safety

Specific Safety Endpoints

1. Adverse Event (AE)
2. Serious Adverse Event (SAE)
3. Death
4. Adverse Drug Reaction (ADR)

5. Serious Adverse Reaction (SAR)
6. Suspected Unexpected Serious Adverse Reaction (SUSAR)

19. Statistical Methods

Analysis of Safety Variables

The protocol states that a secondary study endpoint is: The safety and tolerability of Raltegravir based PrEP in HIV negative individuals

All individuals who received at least one dose of the study drug are included in safety analysis. A total of 38 participants are included.

Drug safety was considered using the endpoints of Adverse Event (AE) and Serious Adverse Event (SAE). The analysis was performed taking a descriptive approach. The proportion that experienced at least one AE or SAE was summarized. The adverse event type, its intensity, and relationship to the study drug was summarized using the number and percentage. In addition, as the total number of adverse events was small, a line listing of each observed event was also produced.

The number and details of any deaths, ADRs, SARs, and SUSARS was described narratively.

20. Summary – Conclusions

20.1 Demographic data

The following tables summarise the demographics of the study population:

Table: Demographic data for all patients (safety population)

		Total population (N=38)
Gender	Male	19 (50.0%)
	Female	19 (50.0%)
Ethnicity;	White or Caucasian	26 (68.4%)
	Black or African	8 (21.1%)
	Oriental	2 (5.3%)
	Other*	2 (5.3%)
Age (years)	Mean, SD (range)	29, 7.5 (20, 54)
BMI (kg/m^2)	Mean, SD (range)[a]	24.2, 3.9 (16.0, 32.7)
Height (m)	Mean, SD (range) [b]	1.73, 0.09 (1.55, 1.91)
Weight (kg)	Mean, SD (range) [b]	72.1, 13.0 (47.1, 97.5)
Systolic blood pressure (mmHg)	Mean, SD (range) [b]	118, 10 (99, 134)
Diastolic blood pressure (mmHg)	Mean, SD (range) [b]	74, 9 (48, 90)
Respiratory rate	Mean, SD (range) [b]	15.8, 1.3 (12, 20)

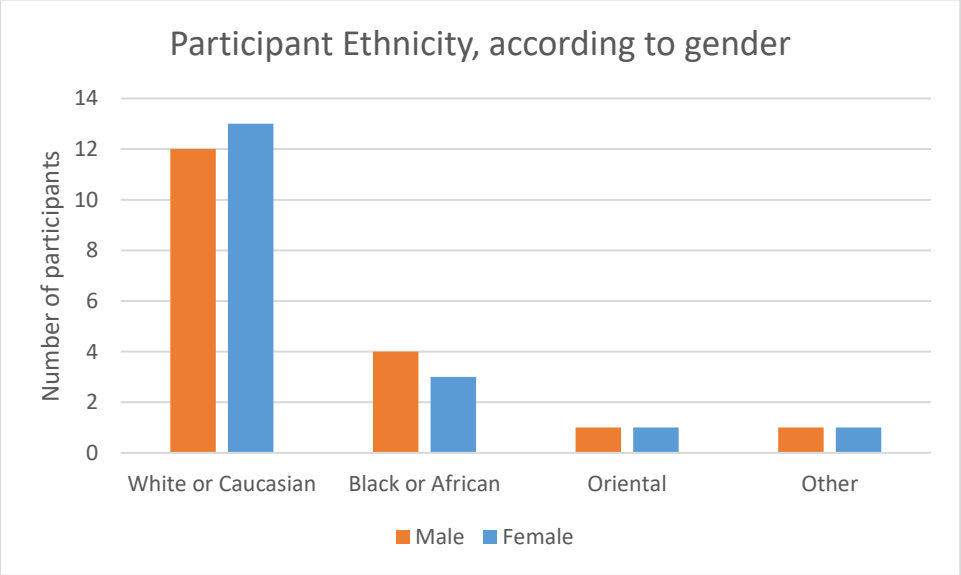
**Asian, n=1 and Mixed n=1* [a]n=36; [b]*n=37*

Table: Baseline characteristics of the per protocol population Frequency (%) is displayed unless otherwise specified.

		Total population (N=36)
Gender	Male	18 (50.0%)
	Female	18 (50.0%)
Ethnicity	White or Caucasian	25 (69.4%)
	Black or African	7 (19.4%)
	Oriental	2 (5.6%)
	Other*	2 (5.6%)
Age (years)	Mean, SD (range)	28, 6.4 (20, 45)
BMI (kg/m^2)	Mean, SD (range)	24.1, 3.9 (16.0, 32.7)
Height (m)	Mean, SD (range)	1.72, 0.09 (1.55, 1.91)
Weight (kg)	Mean, SD (range)	71.6, 13.2 (47.1, 97.5)
Systolic blood pressure (mmHg)	Mean, SD (range)	118, 10 (99, 134)
Diastolic blood pressure (mmHg)	Mean, SD (range)	74, 9 (48, 90)
Respiratory rate	Mean, SD (range)	15.7, 1.4 (12, 20)

**Asian, n=1 and Mixed n=1;* [a]n=34; [b] *n=35*

Figure: Ethnicity of the population



20.2 Primary outcome

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
- 3TC increases the level and longevity of protection in vagina and rectum

Table. Longitudinal level of protection against *ex* vivo challenge in rectal and vaginal tissue explants

Day	Raltegravir		Raltegravir + 3TC	
	Protected rectal tissue (%)	Protected vaginal tissue (%)	Protected rectal tissue (%)	Protected vaginal tissue (%)
0	0.0	0.0	0.0	0.0
2	75.0	83.3	100.0	66.7
4	72.7	66.7	100.0	66.7
6	81.8	83.3	100.0	83.3
8	58.3	66.7	100.0	100.0
10	72.7	83.3	90.9	100.0
12	54.5	66.7	81.8	100.0

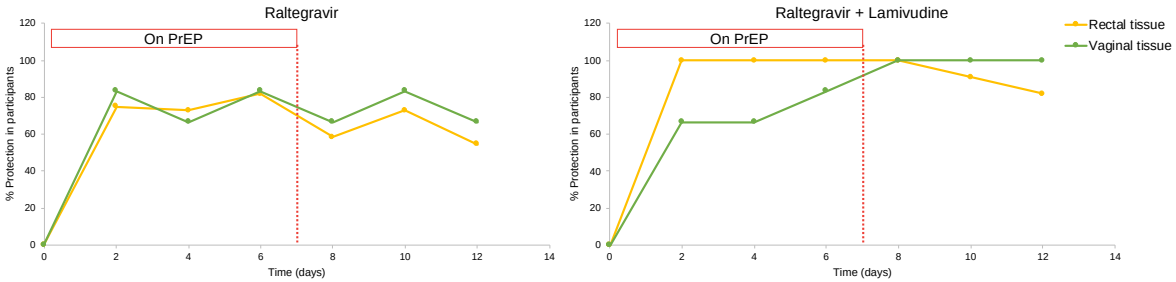


Figure. Longitudinal analysis of level of protection. *Ex vivo protection in r*ectal and vaginal explants was defined as day 15 p24 level >60% lower compared to baseline following challenge with HIV-1_{BaL}. Red doted line indicates time point when PrEP dosing stopped.

Pharmacokinetics

Raltegravir levels:

Table: Raltegravir concentrations in plasma and mucosal tissues following administration of Raltegravir alone (A) and in combination with lamivudine (B)

A

	Raltegravir alone										
Day	Plasma (ng/ml)			VT (ng/g)			VT:Plasma	RT (ng/g)			RT:Plasma
	GM	range		GM	range		GM	GM	range		GM
2	**625.0**	151.1	3494.3	**512.7**	198.8	1273.0	**0.48**	**481.4**	125.2	2593.4	**0.77**
4	**183.9**	6.7	1713.0	**240.7**	38.0	949.4	**0.91**	**748.6**	52.9	12299.1	**4.07**
6	**268.3**	44.3	1626.2	**295.4**	74.0	802.1	**0.70**	**935.4**	201.6	15684.0	**3.49**
8	**273.6**	82.7	1030.2	**168.4**	51.4	784.3	**0.72**	**1003.1**	167.4	33595.3	**3.67**
10	**16.0**	5.3	43.2	**15.3**	6.7	28.7	**0.66**	**179.0**	35.4	2083.9	**28.10**
12	**6.7**	5.3	9.7	**2.6**	0.2	39.6	**5.97**	**118.9**	6.0	10942.0	**28.43**

GM = geometric mean; VT = vaginal tissue; RT = rectal tissue

B

	Raltegravir (+ Lamivudine)										
Day	Plasma (ng/ml)			VT (ng/g)			VT:Plasma	RT (ng/g)			RT:Plasma
	GM	range		GM	range		GM	GM	range		GM
2	**358.8**	50.8	2918.4	**150.8**	20.8	882.9	**0.62**	**577.8**	49.1	2241.8	**1.61**
4	**214.6**	18.4	1129.8	**352.4**	187.8	566.6	**1.13**	**1389.6**	452.7	36186.1	**6.48**
6	**195.0**	71.6	1432.8	**208.1**	93.1	752.2	**0.80**	**368.3**	38.1	4697.5	**1.89**

8	**285.5**	31.4	6358.8	**301.0**	89.3	2802.6	**0.87**	**1226.2**	348.6	21615.2	**4.29**
10	**12.7**	5.8	112.7	**30.7**	14.9	134.5	**1.66**	**1476.9**	60.3	22232.0	**106.47**
12	**12.4**	6.7	35.0	**12.3**	12.3	12.3	**<LLQ**	**133.1**	12.6	3451.7	**24.55**

GM = geometric mean; VT = vaginal tissue; RT = rectal tissue

- Raltegravir was detectable in all tissue samples at day 2 of PrEP administration.
- Raltegravir accumulated in the rectum and continued to persist in this compartment after stopping treatment – geometric mean rectal tissue-to-plasma accumulation ratios were 3.5 on day 6 and 28 on day 12 (raltegravir alone arm)..
- Concentrations in VT were equal to plasma, and plasma explained a greater proportion of the variability in VT level (r2 >0.759; P<0.001) compared with vaginal fluid.
- After PrEP cessation, 50/7% of VT and 86/58% of RT samples remained above raltegravir IC95 (15 ng/mL) at day 10/12.

3TC levels:

Table: Lamivudine concentrations in plasma and mucosal tissues following administration of lamivudine in combination with raltegravir (A)

A

	Lamivudine (+ raltegravir)										
Day	Plasma (ng/ml)			VT (ng/g)			VT:Plasma	RT (ng/g)			RT:Plasma
	GM	range		GM	range		GM	GM	range		GM
2	**184.1**	70.8	900.6	**781.0**	484.4	1301.2	**5.30**	1543.0	725.0	2689.4	**7.86**
4	**142.1**	92.1	214.6	**1400.6**	725.8	2050.8	**9.57**	2773.3	1373.2	11249.1	**19.52**
6	**155.9**	64.9	317.0	**1397.4**	864.1	1929.1	**7.33**	2647.6	702.5	745075.3	**16.98**
8	**170.1**	26.7	1348.8	**1490.8**	1017.7	2336.2	**6.18**	3194.9	884.5	67714.6	**18.78**
10	**14.2**	8.4	29.6	**291.2**	165.1	672.7	**20.63**	936.4	246.6	15351.2	**65.91**
12	**7.8**	3.8	16.9	**101.9**	19.7	289.0	**19.73**	275.4	60.9	4318.6	**49.50**

GM = geometric mean; VT = vaginal tissue; RT = rectal tissue

- Lamivudine exhibited extensive accumulation in both the rectum and female genital tract - geometric mean tissue-to-plasma accumulation ratios were 7.3 (VT) and 17.0 (RT) on day 6.
- Rectal fluid concentrations explained more of the variability for lamivudine in RT (r2 =0.591; p<0.001), than plasma.
- Off PrEP, 3TC persisted in both VT (102 ng/g) and RT (275 ng/g) until day 12.
- Lamivudine-triphosphate levels in VT were 216 pmol/g On PrEP, and 150 pmol/g Off PrEP; However metabolite levels were undetectable in RT.

No gender difference between men and women was observed for PK or PD in rectal tissue

20.3 Safety results

Provide a summary of the number of subjects that experienced an AE, the total number of AEs and SAEs/SARs/SUSARs. Provide details of any deaths.

There was a total of 57 adverse events in 27/38 (71.1%) individuals. There were 13 individuals with one AE, 6 individuals with two AEs, 3 individuals with three AEs, 3 individuals with four AEs, 1 individual with five AEs and 1 individual with six AEs.

There were no deaths during follow-up

Incidence of adverse drug reactions (ADRs): 9 / 57 AEs (15.8%) were assessed as probably or definitely related to at least one study drug in 4 / 38 patients (10.5 %). One individual experienced dehydration and fatigue, one individual experienced acid reflux and dizziness, one individual experienced vivid dreams on one occasion, and one individual experienced vivid dreams on two occasions.

There were 0 Serious Adverse Reactions (SARs), 0 unexpected SARs and 0 SUSARs.

		Total study participants (n=38)
Had at least one AE		27 (71.1%)
Had at least one SAE		0 (0.0%)
Total number of AEs	0 1 2 3 4 5 6	11 (28.9%) 13 (34.2%) 6 (15.8%) 3 (7.9%) 3 (7.9%) 1 (2.6%) 1 (2.6%)
		Total adverse events (n=57)
Adverse event type	Respiratory, thoracic and mediastinal disorders Gastrointestinal Disorders Psychiatric Disorders General Disorders and Administration Site Disorders Nervous System Disorders Infection and Infestation Blood and Lymphatic System Disorders	11 (19.3%) 10 (17.5%) 7 (12.3%) 6 (10.5%) 6 (10.5%) 5 (8.8%) 4 (7.0%)
	Neoplasms benign, malignant and unspecified Vascular Disorders Injury, Poisoning and Procedural Complaints Investigations Musculoskeletal and tissue disorders Skin and subcutaneous tissue disorders	2 (3.5%) 2 (3.5%) 1 (1.8%) 1 (1.8%) 1 (1.8%) 1 (1.8%)
Intensity	Mild Moderate Severe	36 (63.2%) 20 (30.1%) 1 (1.8%)
Relationship to study drug	Unrelated Unlikely Possible Probable Definite	34 (59.7%) 10 (17.5%) 4 (7.0%) 7 (12.3%) 2 (3.5%)

Table: Listing of Adverse Events for all patients

Table: Listing of Serious Adverse Events for all patients

No Serious Adverse Events were reported
No deaths were reported

Within the per protocol population (n= 36), a total of 52 AEs, including “0” SAE, were identified as treatment-emergent and included in the safety analysis. Summary tables for AEs and SAEs are presented in the appendix of this synopsis.

Overall, 25 patients (69.4%) patients experienced at least one AE. The proportion that experienced at least one SAE was 0% (n=0).

Incidence of adverse drug reactions (ADRs): 5 / 52 AEs (9.6%) were assessed as probably or definitely related to at least one study drug in 3 / 36 patients (8.3 %). One individual experienced dehydration and fatigue, one individual experienced vivid dreams on one occasion, and one individual experienced vivid dreams on two occasions.

There were 0 Serious Adverse Reactions (SARs), 0 unexpected SARs and 0 SUSARs.

20.4 Conclusion

- Raltegravir and Raltegravir/3TC PrEP was well tolerated
- Rapid protection was observed in both arms with addition of 3TC leading to greater protection from HIV-1 in rectum and longer and greater protection in vaginal tissue
- These data support further investigation of these agents for PrEP
- Possible PrEP indication for Raltgravir/3TC: individuals intolerant of Truvada
- 3TC data provides more evidence for its use as a FTC PrEP alternative
- Following discontinuation, high concentrations of RGV remained in RT (but rapid decline in plasma and VT concentrations) with persistent inhibitory activity in RT up to 4 days later. Addition of lamivudine increased inhibitory activity in RT and VT, with similar persistent inhibition associated with high 3TC RT concentrations 4 days after discontinuation.

21. Date of Report

This is version 1.0 of the Clinical Study Report synopsis, dated 15/Nov/2019.

APPENDICES

i) Summary of treatment-emergent AEs in the per protocol population

		Total study participants (n=36)
Had at least one AE		25 (69.4%)
Had at least one SAE		0 (0.0%)
Total number of AEs	0 1 2 3 4 5 6	11 (30.6%) 12 (34.2%) 6 (16.7%) 3 (8.3%) 2 (5.6%) 1 (2.8%) 1 (2.8%)
		Total adverse events (n=52)
Adverse event type	Respiratory, thoracic and mediastinal disorders Gastrointestinal Disorders Psychiatric Disorders General Disorders and Administration Site Disorders Nervous System Disorders Infection and Infestation Blood and Lymphatic System Disorders	11 (21.2%) 8 (15.4%) 6 (11.5%) 6 (11.5%) 4 (7.7%) 5 (9.6%) 4 (7.7%)
	Neoplasms benign, malignant and unspecified Vascular Disorders Injury, Poisoning and Procedural Complaints Investigations Musculoskeletal and tissue disorders	2 (3.9%) 2 (3.9%) 1 (1.9%) 1 (1.9%) 1 (1.9%)

	Skin and subcutaneous tissue disorders	1 (1.9%)
Intensity	Mild Moderate Severe	32 (61.5%) 19 (36.5%) 1 (1.9%)
Relationship to study drug	Unrelated Unlikely Possible Probable Definite	33 (63.5%) 10 (19.2%) 4 (7.7%) 3 (5.8%) 2 (3.9%)

Line listing of observed Adverse Events – Per Protocol Population

ID	SOC_coding	Description	Status	Days to resolve	Concommitent medicine given	Intensity	Study drug action	Outcome	Rela to s
1	Muscularskeletal and tissue disorders	Painful left toe	New AE		Yes	Moderate	Agent Dose Not Changed	Resolving	Unr
1	Infection and Infestation	Viral illness with abdominal pain, vomiting, nausea, fever	New AE		No	Moderate	Agent Dose Not Changed	Resolving	Unli
2	Nervous System Disorders	headache	New AE	1	Yes	Moderate	Agent Dose Not Changed	Resolved	Unli
2	Respiratory, thoracic and mediastinal disorders	nose bleed	New AE	0	No	Mild	Agent Dose Not Changed	Resolved	Unr
3	Respiratory, thoracic and mediastinal disorders	Runny nose	New AE	14	No	Mild	Agent Dose Not Changed	Resolved	Unr
8	Gastrointestinal Disorders	Loose stool	New AE	9	No	Mild	Agent Dose Not Changed	Resolved	Pos
9	Respiratory, thoracic and mediastinal disorders	cold	Ongoing AE no change		Yes	Moderate	Agent Dose Not Changed	Resolving	Unr
10	Respiratory, thoracic and mediastinal disorders	Runny nose	New AE		Yes	Mild	Agent Dose Not Changed	Resolving	Unr
12	General Disorders and Administration Site Disorders	Fatigue	New AE	6	No	Mild	Agent Dose Not Changed	Resolved	Prol
12	General Disorders and Administration Site Disorders	Dehydration	New AE	0	No	Mild	Agent Dose Not Changed	Resolved	Prol
12	General Disorders and Administration Site Disorders	Rectal Pain	New AE	0	Yes	Moderate	Agent Dose Not Changed	Resolved	Unr
12	Gastrointestinal Disorders	Diarrhoea	New AE	1	No	Mild	Agent Dose Not Changed	Not resolved	Unr
12	Neoplasms benign, malignant and unspecified	Perianal lump (haemorrhoid)	New AE		No	Moderate	Agent Dose Not Changed	Not resolved	Unr
12	Gastrointestinal Disorders	Diarrhoea/Faecal incontinence	New AE	1	No	Moderate	NA	Resolved	Unli
14	Vascular Disorders	Vaginal spotting	New AE	31	No	Mild	Agent Dose Not Changed	Resolved	Unr

16	Skin and subcutaneous tissue disorders	Folliculitis	New AE	26	Yes	Moderate	Agent Dose Not Changed	Resolving	Unr
16	Gastrointestinal Disorders	Diarrhoea	New AE	2	Yes	Moderate	Agent Dose Not Changed	Resolved	Unli
18	Respiratory, thoracic and mediastinal disorders	Runny Nose	New AE		No	Mild	NA	Not resolved	Unr
19	Psychiatric Disorders	Vivid dreams	New AE	6	No	Mild	Agent Dose Not Changed	Not resolved	Defi
19	Psychiatric Disorders	Vivid dreams	New AE	8	No	Mild	Agent Dose Not Changed	Resolved	Defi
19	General Disorders and Administration Site Disorders	Chills/feeling unwell	New AE	7	Yes	Moderate	Agent Dose Not Changed	Resolved	Unr
20	Nervous System Disorders	Headache	New AE	1	No	Mild	Agent Dose Not Changed	Resolved	Unli
23	Infection and Infestation	Flu-like illness	New AE		No	Moderate	Agent Dose Not Changed	Resolving	Unr
24	Respiratory, thoracic and mediastinal disorders	Runny nose (Sniffle)	New AE	34	Yes	Moderate	Agent Dose Not Changed	Resolved	Unr
27	General Disorders and Administration Site Disorders	Fatigue	New AE	25	No	Mild	Agent Dose Not Changed	Resolved	Unr
27	Blood and Lymphatic System Disorders	Swollen left post-auricular lymph gland	New AE	25	No	Mild	Agent Dose Not Changed	Resolved	Unr
27	Infection and Infestation	Tonsillitis	New AE	18	Yes	Moderate	NA	Resolved	Unr
27	Respiratory, thoracic and mediastinal disorders	Cough	New AE		No	Mild	Agent Dose Not Changed	Resolving	Unr
28	Infection and Infestation	Tonsillitis	New AE	3	Yes	Moderate	Agent Dose Not Changed	Resolved	Unr
28	Respiratory, thoracic and mediastinal disorders	Sore throat	New AE	14	Yes	Moderate	Agent Dose Not Changed	Resolved	Unr
29	General Disorders and Administration Site Disorders	Fatigue	New AE	14	Yes	Mild	NA	Resolved	Unr
29	Blood and Lymphatic System Disorders	Neck lump right side	New AE	20	No	Mild	Agent Dose Not Changed	Resolved	Unr
29	Investigations	rectal discomfort and PR bleeding lasting more than 24	New AE	6	No	Mild	Agent Dose Not Changed	Resolved	Unr
29	Infection and Infestation	Fever	New AE	2	Yes	Moderate	Agent Dose Not Changed	Resolved	Unr

30	Injury, Poisoning and Procedural Complaints	Fluoxetine overdose			No	Severe	Agent Dose Not Changed	Resolved	Unr
33	Blood and Lymphatic System Disorders	Abnormal LFT's	New AE	129	No	Mild	Agent Dose Not Changed	Resolved	Unli
33	Respiratory, thoracic and mediastinal disorders	Sore throat	New AE	8	No	Mild	Agent Dose Not Changed	Resolving	Unli
33	Gastrointestinal Disorders	Nausea	New AE	0	No	Mild	Agent Dose Not Changed	Resolved	Unli
34	Vascular Disorders	Spotting	New AE	42	No	Mild	NA	Resolved	Unr
34	Nervous System Disorders	Light headedness	New AE		No	Mild	Agent Dose Not Changed	Resolving	Unr
36	Nervous System Disorders	Headache	New AE	0	Yes	Moderate	Agent Dose Not Changed	Resolved	Unr
36	Blood and Lymphatic System Disorders	swollen neck glands	New AE	12	No	Moderate	Agent Dose Not Changed	Resolved	Unr
36	Gastrointestinal Disorders	Diarrhoea	New AE	2	No	Mild	Agent Dose Not Changed	Resolving	Unli
36	Gastrointestinal Disorders	Diarrhoea	New AE	2	No	Mild	Agent Dose Not Changed	Resolved	Poss
36	Gastrointestinal Disorders	Impacted tooth	New AE	4	No	Moderate	NA	Not resolved	Unr
38	Respiratory, thoracic and mediastinal disorders	cold symptoms	New AE	7	Yes	Mild	Agent Dose Not Changed	Resolved	Unr
42	Neoplasms benign, malignant and unspecified	Perianal cyst	New AE		No	Mild	Agent Dose Not Changed	Not resolved	Unr
42	Psychiatric Disorders	sleep disturbance	New AE	31	No	Mild	Agent Dose Not Changed	Resolved	Unli
43	Psychiatric Disorders	vivid dreams	New AE	5	No	Mild	Agent Dose Not Changed	Resolved	Prol
45	Psychiatric Disorders	nightmares and vivid dreams	New AE	4	No	Mild	Agent Dose Not Changed	Resolved	Poss
45	Psychiatric Disorders	vivid dreams	New AE	1	No	Mild	Agent Dose Not Changed	Resolved	Poss
45	Respiratory, thoracic and mediastinal disorders	headache blocked nose, fever	New AE	9	Yes	Mild	Agent Dose Not Changed	Resolving	Unr

ii) Summary of treatment-emergent ARs in the per protocol population

iii) Summary of treatment-emergent SAEs in the study population

There were no SAEs in the study population

iv) Summary of treatment-emergent SARs in the study population

There were no SARs in the study population