PROTOCOL FULL TITLE:

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

Protocol Short Title/Acronym

R-PrEP

Trial Identifiers:

EudraCT Number – 2016-000437-43

REC Number – 17/LO/0094

Sponsor

Name: Guy's and St Thomas' NHS Foundation Trust

Address: King's Health Partners Clinical Trials Office, F16 Tower Wing Guys Hospital, Great Maze Pond, London SE1 9RT

Telephone: 020 7188 5732

Fax: 020 7188 8330

Email: R&D@gstt.nhs.uk

Chief Investigator

Name: Julie Fox

Address: Harrison Wing, 2nd Floor Lambeth Wing, St Thomas' Hospital Westminster Bridge Road, London SE1 7EH

Telephone: 020 7188 2643

Fax: 020 7188 2646

Email: Julie.Fox@kcl.ac.uk

Co-Investigator(s), Statistician, Laboratories

Name: Professor Robin Shattock (pharmacodynamics)

Address: Department of Medicine, St Mary's Campus, Imperial College London

Telephone: 020 7594 2510

Fax: 020 7504 2699

Email: r.shattock@imperial.ac.uk

Name: Dr Carolina Herrera, (pharmacodynamics)

Address: Imperial College, St Mary's Campus, Imperial College London

Telephone: 020 7594 2545

Fax: 020 7504 2699

Email: c.herrera@ic.ac.uk

Name: Dr Laura Else (pharmacokinetics)

Address: Pharmacology Research Laboratories, Block H – First floor, 70 Pembroke Place, Liverpool, L69 3GF

Phone: 0151 794 5553

Fax: 0151 794 5656

Email: l.else@liv.ac.uk

Name: Professor Saye Khoo (pharmacokinetics)

Address: Pharmacology Research Laboratories, Block H – First floor, 70 Pembroke Place, Liverpool, L69 3GF

Phone: 0151 794 5547

Fax: 0151 794 5656

Email: s.khoo@liv.ac.uk

Name: Vanessa Tierney (Statistics)

Address: Biometrics Lead, St Stephen's Clinical Research
St Stephen's AIDS Trust, 369 Fulham Road, London SW10 9NH

Phone:

Fax:

Email: vanessa.tierney@ststcr.com

1. 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	Phase IV
Sponsor name	Guy's and St Thomas' NHS Foundation Trust
Chief Investigator	Julie Fox
Eudract number	2016-000437-43
REC number	
Medical condition under investigation	HIV
Purpose of clinical trial	To investigate the role of Raltegravir +/- lamivudine in HIV prevention

Aims	For each regimen (Raltegravir versus Raltegravir/lamivudine) we have the following aims: 1. To determine the level of drug required in the plasma, vagina and rectum for mucosal *ex vivo* protection from HIV 2. To determine the time from first dose of drug to mucosal *ex vivo* protection from HIV infection 3. To determine the time to cessation of mucosal *ex vivo* protection from HIV after stopping ART at steady state. 4. 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 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
Sample Size	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)	None
Maximum duration of treatment of a subject	7 days Raltegravir 400mg bd followed by minimum 4 weeks wash out and then 7 days Raltegravir 400mg/lamivudine 150mg (oral tablets) bd. Or vice versa.
Version and date of final protocol	V1.2 03/04/17
Version and date of protocol amendments	V1.3 23/11/18

2. 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

TMG – trial management group

U&Es – urea & electrolytes

WCC – white cell count

CONTENTS

3. Background & Rationale

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.

The team:

The applicants are highly experienced in carrying out such studies and collaborating together. Dr Fox is Chief Investigator on similar PrEP studies and is highly experienced in running clinical trials. Professor Shattock and Dr Herrera are world renown for their pioneering work in HIV prevention and pioneered the use of explant models to quantify HIV infectivity. Professor Khoo and Dr Boffito are world renown for their pharmacokinetic work in novel drugs and HIV prevention. The volunteers for similar studies remain in touch with the unit via newsletters and patient representatives are involved with study design and protocol development.

Hypothesis

We hypothesize that a 7- day course of Raltegravir given either with or without lamivudine will produce adequate drug levels of Raltegravir in genital tissue to provide *ex vivo* protection from HIV infection.

4 Trial Objectives and Design

4.1. Trial Objectives

For each drug (Raltegravir and lamivudine) we have the following aims:

1. To determine the level of drug required in the plasma, vagina and rectum for mucosal *ex vivo* protection from HIV
2. To determine the time from first dose of drug to mucosal *ex vivo* protection from HIV infection
3. To determine the time to cessation of mucosal *ex vivo* protection from HIV after stopping ART at steady state.
4. To determine the safety and tolerability of Raltegravir based PreP in HIV negative individuals

4.1.1 Primary endpoints

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

4.1.2 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

4.2 Trial Design

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.

Substudy: To determine the decay kinetics of Raltegravir following cessation at steady state.

All participants will be offered the chance to participate in the sub study, but their participation is optional. Participants who consent to the optional sub study will be required to provide paired plasma, urine & saliva samples which will be collected on day 8,9,10 from ARM B and day 42,43,44 from ARM A. If Sub study sampling days fall on main study visit days, sampling can be obtained the same time. Should sub study visits fall over a weekend, visits can be postponed accordingly. Date and time of sampling will be recorded and sent with samples for analysis.

Recruitment:

Recruitment will take place at Guys and St Thomas' NHS Trust Hospital. . Recognizing that anal sex is a route of transmission for heterosexuals, women will undertake vaginal and rectal sampling. The Site has carried out many similar tissue sampling studies.

4.3 Trial Flowchart

Figure 1: Flow chart to summarize the visit schedule

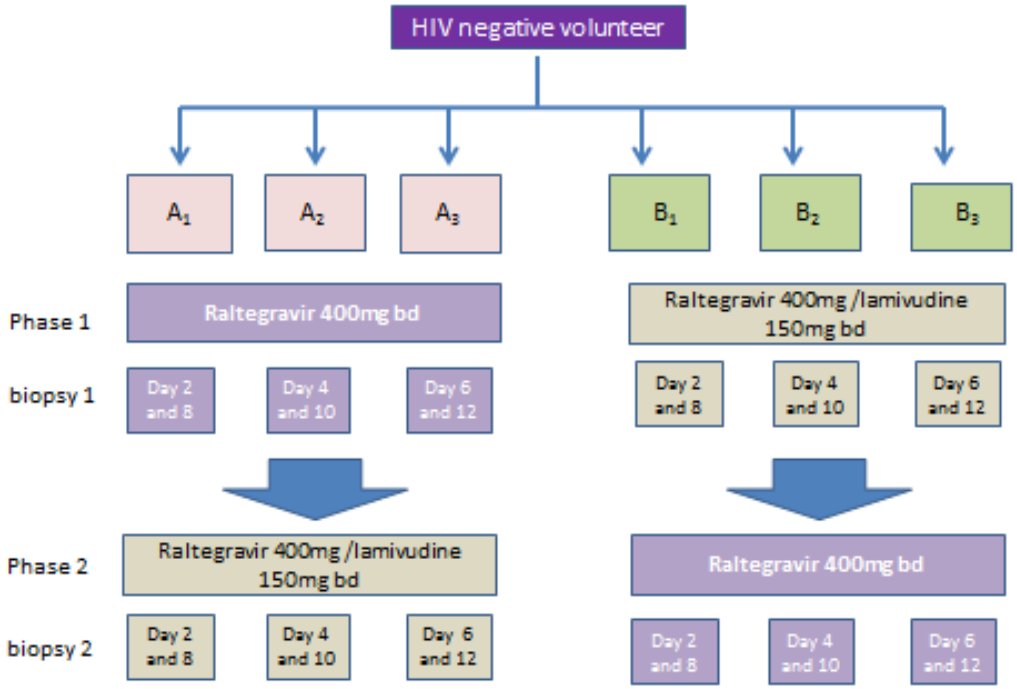

Table 1: visit schedule

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															
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

WASH OUT PERIOD

*fasted

**genital swabs: vaginal (women only), rectal (women and men)

Women may need to attend for baseline biopsies on a separate day from ART initiation due to menstrual cycle factors (ie biopsies should not be taken around menstruation and the luteal phase should be targeted where possible).

***PD sample only**

Women may need to attend for baseline sampling on a separate day from Baseline visit due to menstrual cycle factors (ie biopsies should not be taken around menstruation and the luteal phase should be targeted where possible).
Once randomisation has occurred and study drug dispensed, participants will be informed when to take their first dose to ensure timelines between first dose and sampling are adhered to, based on their randomisation group.

Table 1a: Substudy Visit schedule

	ARM B			ARM A		
Day*	**8**	**9**	**10**	**42**	**43**	**44**
Plasma	x	x	x	x	x	X
Urine	x	x	x	x	x	X
Saliva	x	x	x	x	x	x

.* Should any sub study days coincide with a weekend, visits can be postponed accordingly.

5 Trial Medication

5.1 Investigational Medicinal Products

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

Raltegravir is being supplied by Merck to the sponsor site. The sponsor site will distribute the raltegravir to the other recruiting sites.
Lamivudine will be supplied from hospital commercial stock at each site.
All drugs will be dispensed by the pharmacy department of the participating centres against a Trial Specific Prescription. A R-Prep prescription will be supplied by the sponsor but sites may wish to use their own prescription template (a copy of which should be provided to the sponsor).

The medication will be packed down into the required quantities and a trial-specific, Annex 13 compliant label attached at the point of dispensing.

5.2 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.

5.3 IMP Risks

The SmPC for Isentress® and Lamivudine will act as the reference documents. We do not anticipate any interaction concerns.

5.4 Drug Accountability

Each local pharmacy must maintain accurate accountability records of the IMP, including but not limited to the quantity received, the quantity dispensed to which subject, batch number, expiry date, study drug returns and the date of each transaction. Participants will be asked to return empty packaging to the pharmacy for accountability. Study drug returns must be verified by the study monitor prior to disposal.

R-Prep Accountability Log will be provided by the sponsor, but sites may wish to use in house logs (a copy of which should be provided to the sponsor).

5.5 Storage of IMP

Raltegravir (Isentress®) does not require any special storage conditions (as per SmPC)

Lamivudine – store < 30°C

5.6 Subject Compliance

The administration of ART will be planned between the participant and study nurse. The participant will take the morning dose at 11am and the evening dose at 11pm. The sampling must occur fasted and prior to that day's morning dose of study drug.

5.7 Concomitant Medication

All concomitant medication will be recorded. Concomitant therapies will be managed in line with the Summary of Product Characteristics guidance for Isentress® 400mg tablets and Lamivudine 150mg tablets.

6 Selection and Withdrawal of Subjects

6.1 Inclusion Criteria

Participants must satisfy all of the following criteria prior to the baseline visit:

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.

6.2 Exclusion Criteria

1. Any significant acute or chronic medical illness.
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 syphilis, hepatitis B (HBs Ag) and/or C antibodies.
4. Positive blood screen for HIV antibodies.
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): had unprotected vaginal or anal sex with a known HIV infected person or a casual partner. engaged in sex work for money or drugs. acquired a bacterial sexually transmitted disease in the past 3 months. having a known HIV positive partner either currently or in the previous six months Females who are pregnant or breast-feeding.
7. Clinically significant laboratory abnormalities (according to normal range as defined by central laboratory).
8. Participation in a clinical trial of an Investigational product within 1 month of planned baseline enrolment in this study.
9. Ingestion of H2 receptor antagonists or proton pump inhibitor drugs in the preceding 14 days
10. Current of planned use of anti-epileptics

6.3 Selection of Participants

Healthy adult volunteers will be recruited through information presented in community organisations, hospitals, colleges, other institutions and/or advertisements, including email responses to expressed interest. The content of these advertisements will be included in the

submission to the Research Ethics Service, for approval. This information will contain contact details for the units conducting the study.

During the recruitment process, interested volunteers will be provided with a participant information sheet, detailing the trial, its procedures and medication to be investigated and given time to consider their participation prior to arranging an appointment for a screening visit. Potential participants will be given a minimum of one day to review the information sheet and ask questions relating to trial participation, but can have as long as the trial remains open for recruitment. At the screening visit, before undertaking any screening procedures, volunteers will be able to discuss the trial to ensure they have enough information to confirm their written informed consent. An important part of the screening history will involve assessment of HIV risk, and all trial staff will be experienced healthcare practitioners, trained in the conduct of clinical research and capable of conducting such a discussion.

6.4 Randomisation Procedure / Code Break

Individuals will be randomized according to gender into one of 6 groups 1:1:1:1:1:1 randomisation and within, with randomisation/allocation to study arm being determined using the MedSciNet eCRF randomisation function. This is not a blinded study therefore patients and research team will know what medications the patient is receiving.

6.5 Withdrawal of Subjects

Participants have the right to withdraw from the trial at any time for any reason. The investigator may also withdraw participants from the trial in the event of inter-current illness, adverse events, protocol violations, administrative reasons or other reasons. An excessive rate of withdrawals can render the trial impossible to interpret; therefore unnecessary withdrawal of participants should be avoided. Those withdrawing prior to the second phase will be replaced and new participants will be allocated to the same treatment arm as the individual who withdrew from the study. These new participants will start from baseline. Participants withdrawing from the trial will be asked to attend for a withdrawal visit.

In all cases the date and reasons for withdrawal or withholding the dose of medication will be clearly stated on the participant's CRF. If the reason for removal of a participant from the trial is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded on the CRF.

6.6 Expected Duration of Trial

The trial is expected to last 7 months. Starting from first patient first visit and the end of the trial will be considered the last patient's last visit.

As the visit windows are generous, the total duration of involvement will vary for each patient. From signing consent to completing the trial, patients will be involved for approximately 8 weeks.

7 Trial Procedures

7.1 By Visit

Individuals attend for 8 visits. Once screened the remaining 7 visits will take place over approximately an 8 week period.

Assessments at each visit

The schedule of assessments is summarised in the trial flow chart.

During the study, participants will be instructed to refrain from certain activities:

- strenuous exercise or marked increases in current exercise activity
- sexual intercourse as per inclusion criteria and anal and vaginal products and preparations as per inclusion criteria for 48 hours prior to and post each scheduled sample/biopsy collection.
- donating blood
- engaging in high-risk behaviour for HIV infection as per inclusion criteria
- taking part in another drug trial for the duration of the study

Visit 1: Screening Visit

Prior to the screening visit participants will be provided with written information about the trial in the form of a participant information sheet and will be allowed adequate time for questions and to consider the trial before agreeing to participate. It will be the responsibility of the investigator or co-investigator to obtain written informed consent prior to undertaking any procedures detailed in the protocol.

The investigator or designee must provide adequate explanation of the aims, methods, objectives and potential hazards of the trial. It must also be explained to the participant that they are free to refuse or withdraw from the trial for any reason without detriment to their future care or treatment.

Possible eligible and interested participants will be asked to volunteer their participation in this trial. Willing participants will be required to read, sign and date an informed consent document prior to any trial related procedures being performed.

Participants will be given the opportunity to ask any questions regarding the trial at this stage and throughout the whole trial period.

If the volunteer agrees to participate, site personnel will perform an HIV risk assessment (see exclusion criteria number 6) and an HIV blood test. Any volunteers found to be infected with HIV at screening will be managed as described in section 7.2.

Screening evaluations will be used to determine the eligibility of each candidate for trial enrolment. Following informed consent, the screening visit will evaluate:

- HIV risk assessment (as per inclusion / exclusion criteria)
- Demographic details (age, gender, ethnic origin)
- Full medical, drug and social history
- Directed Physical examination including examination of skin, weight, height, and vital signs (temperature, blood pressure, heart rate and respiratory rate)
- Brief external genitalia examination
- Blood tests:
    - HIV antibody testing and discussion

  - Hepatitis B (surface antigen), Hepatitis C (antibody)
  - Syphilis Screening
  - Biochemistry (U&E, ALT) and haematology
- Urine ßhCG for women- for females of childbearing potential

- Urine and self-administered rectal swab for Chlamydia and gonorrhoea testing for men
- Self-administered vaginal and rectal swab for Chlamydia and gonorrhoea testing for women
- Concomitant medications
- Women will be asked at enrolment if they have any vaginal discharge and men if they have any rectal or urethral discharge. If they do they will be asked to attend a sexual health clinic. If their symptoms are not caused by a sexually transmitted infection and have resolved by the time of visit 2, they will be able to proceed with the study. Patients will be asked to attend a sexual health clinic if they have vaginal, rectal or urethral symptoms at any further point during the study and to report this to the study co-ordinator.

For women, the baseline visit will be scheduled for a time that avoids menstruation. If a female is menstruating the visit will be delayed until after menstruation has completed and around the luteal phase where possible.

Individuals will be informed that the tissue pharmacodynamics analysis can only be performed on fresh tissue and therefore biopsies at the baseline visit and any subsequent ones must be taken in the morning.

Randomisation will take place once screening evaluations have confirmed eligibility, and it has been confirmed that individuals are still willing to take part in the study. This will occur prior to any baseline procedures.

Visit 2: Baseline (3-42 days from screening):

Women may need to attend for baseline sampling on a separate day from Baseline visit due to menstrual cycle factors (ie biopsies should not be taken around menstruation and the luteal phase should be targeted where possible). The on ART and off ART biopsies visits must not occur during menstruation. The maximum time between baseline visit and sampling is 6 weeks.

Participants will be instructed to attend the research unit at a specified time.
The following evaluations will be performed in the morning of Day 0, before trial medication dosing and tissue sampling:

- Randomisation
- Physical / genital exam if clinically indicated
- Vital signs (temperature, blood pressure, heart rate, and respiratory rate)
- Concomitant medications review
- Urine ßhCG - for females of childbearing potential
- Progesterone (women only)

Tissue samples (pharmacodynamics only):
Men: Rectal tissue biopsy
Women: vaginal and rectal tissue biopsies

Visit 2: ART initiation (post sampling)
This may occur on the same day as visit 2. For women, this is providing that the estimated date of menstruation will not impact subsequent biopsy visits. If this occurs, the day of ART initiation should be soon after menstruation has finished.

Visit 3,4,6,7: Sample collection. Fasting trough levels to be taken prior to that day's morning dose

The following evaluations will take place prior to sampling:

- Confirmation of time that participant administered Raltegravir 400mg +/-lamivudine
- Physical / genital exam if clinically indicated
- Vital signs (temperature, blood pressure, heart rate, and respiratory rate)
- Concomitant medications review
- Adverse event review. If significant adverse events have been reported, these will be clinically followed in accordance to the instruction of the study physician.
- Blood and tissues samples for routine safety analysis and research purposes will be taken as follows:

PK samples:

- Plasma will be extracted from 6mls of blood for drug level analysis
- 2 x saliva sample for men and women
- 2 x Vaginal swab for women
- 2 x rectal swab for men and women
- 5-6 x Rectal tissue for men and women
- 5-6 x Vaginal tissue for women

- Progesterone (women only)
- Urine ßhCG - for females of childbearing potential (visit 7 only)

Visit 5:

For women, this visit will occur soon after menstruation has finished so that subsequent tissue sampling visits will avoid menstruation.

The following evaluations will take place prior to sampling:

- Directed Physical / genital exam if clinically indicated
- Vital signs (temperature, blood pressure, heart rate, and respiratory rate)
- Concomitant medications review
- Adverse event review. If significant adverse events have been reported, these will be clinically followed in accordance to the instruction of the study physician.
- Urine ßhCG - for females of childbearing potential

ART will be prescribed.

Visit 8: Follow-up visit/withdrawal visit (3 days to 14 days after visit 7)

Participants will attend for:

- Concomitant medications review
- Adverse event review
- Genital and physical examination if clinically indicated

Substudy (Optional)

Participants consenting to the Substudy will need to attend for the following:

- Upon discontinuation of Raltegravir + lamivudine, 3 consecutive days of sampling:
- Arm B: Days 8, 9 & 10
- Arm A: Days 42, 43 & 44.
  PK samples to be obtained:
  - plasma (6mls),
  - urine (10mLs)
  - saliva (3mLs)

  If any of the substudy sampling days fall on main study visit days, sampling can be done at the same time.

7.2 Laboratory Tests

Safety analysis samples

At screening, blood will be drawn for chemistry, haematology & viral serology together with urine (dipstick for pregnancy) samples. Samples will be analysed locally.

All results will be in written in the source and eCRF. The investigator must review, sign and date the laboratory results/reports, comment whether any abnormal values are clinically significant and record any clinically relevant changes occurring during the study in the adverse event section of the CRF.

STI screening: The Gen-Probe Aptima test (for chlamydia and gonorrhoea) will be used on first void urine and self-collected rectal swab in men and self-collected vaginal and rectal swab for women. Samples will be analysed locally.

HIV risk assessment, HIV testing/discussion, and treatment in case of a positive HIV test

Site personnel will assess volunteers for past and current risk of HIV infection. Additionally, site personnel will perform pre-HIV test counselling (prior to collecting blood for an HIV test) and post-HIV test counselling (when HIV test results are available). Samples will be analysed locally. In the event of a volunteer being diagnosed HIV positive at screening they will immediately be referred to the HIV clinic for further counselling and engagement into HIV services.

Research samples

Research PK samples are taken at visit 3,4,6,7.

- 9mls blood will be drawn: 25µL of whole blood will be used for dry blood spot. Plasma will be extracted from the remainder of the 9mls and transported to Liverpool University for PK analysis with dry blood spot card.
- Oral fluid sample – saliva will be extracted from 2 x Salivette samples and transported to Liverpool University for PK analysis

- Genital tract sampling:
  - For men: 2 rectal swabs using a WEKs sponge followed by 5-6x 1mm^3 rectal biopsies taken from the wall of the rectum
  - For women: 2x cervico-vaginal swabs, 2 rectal swabs, followed by 5-6 x 1mm^3 vaginal biopsies taken from the wall of the vagina and 5-6x 1mm^3 rectal biopsies taken from the wall of the rectum

Sample analysis:

- Raltegravir and lamivudine drug levels will be measured at Liverpool University

- Quantification of protection from HIV infection: will be carried out by Professor Shattock's laboratory at Imperial College London. Biopsy tissue will be exposed to different concentrations of HIV virus (BAL R5), washed and cultured for 15 days. Cultures wil be fed at days 3, 7, 11 and 15 when culture supernatant will be harvested and frozen prior to addition of fresh media. HIV p24 Ag ELISA measurements will be carried out for detection of antigen in culture supernatants though out the 15 days of culture. Evaluation of the viral replication kinetics during culture (p24 at days 3, 7, 11 and 15) and level of p24 at day 15 will allow us to assess if the initial ex vivo inoculum has been able to replicate in the tissue following in vivo dosing.

Safety blood tests, STI tests, research sampling and processing:

- Harrison Wing, 2nd floor Southwark Wing, Guy's Hospital, Great Maze Pond, London, SE1 9RT

Pharmacokinetics (drug levels)

Pharmacology Research Laboratories, Block H – First floor, 70 Pembroke Place, Liverpool, L69 3GF

Pharmacodynamic analysis (vaginal and rectal tissue)

Professor Robin Shattock, 4th floor Medical School, Imperial College- St Mary's Hospital
1 Norfolk Place, London, W2 1PG

8 Assessment of Efficacy

8.1.1 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.

8.1.2 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

9 Assessment of Safety

9.1 Specification, Timing and Recording of Safety Parameters.

Subject safety will be determined by physical examination, blood tests and adverse event reporting. FBC, U&E and LFTs will be carried out at baseline and thereafter as symptom directed.

9.2 Management of potential adverse outcomes after tissue biopsies

Study participants will be given information regarding which symptoms should alert them to the possibility of perforation or major bleed following their biopsies. In the event of these symptoms they will be advised to attend their local Accident & Emergency Department directly and to take with them their Patient Information Card and/or inform

the medical staff that they are participating in a study at the Harrison Wing research unit or SSAT involving rectal biopsies and that the research unit needs to be informed of their admission.

9.3 Procedures for Recording and Reporting Adverse Events

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:

The summary of product characteristics (SmPC) for that product (for products with a marketing authorisation)

Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

Results in death;
Is life-threatening;
Required hospitalisation or prolongation of existing hospitalisation;
Results in persistent or significant disability or incapacity;
Consists of a congenital anomaly or birth defect.

Although not a serious adverse event, any unplanned pregnancy should be reported via

the SAE reporting system as stated below.

Reporting Responsibilities

Guy's & St. Thomas' NHS Foundation Trust have delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the King's Health Partners Clinical Trials Office (KHP CTO).

All SAEs, SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) will be reported immediately (and certainly no later than 24 hours) by the Principal Investigator to the Chief Investigator who will review and report to the KHP-CTO in accordance with the current Pharmacovigilance Policy.

The KHP CTO will report SUSARs to the regulatory authorities (MHRA, competent authorities of other EEA (European Economic Area) states in which the trial is taking place.

The Chief Investigator will report to the relevant ethics committee. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.
- The Chief Investigator and KHP CTO (on behalf of the sponsor), will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually.

9.3.1 Adverse events that do not require reporting

Raltegravir and lamivudine are licenced drugs in HIV infected individuals. However as this study concerns HIV negative individuals all events or reactions will be reported from randomisation until the final visit.

9.4 Treatment Stopping Rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator, ethics committee concerned or Regulatory Authority on the basis of new safety information.

If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected.

10 Statistics

This randomised study contains a larger number of individuals per arm than most other HIV PK/PD studies. Therefore bias is significantly reduced to a minimum. Each patient is their own control hence bias is further reduced. There will be an equal number of men and women in each arm.

10.1 Sample Size

The number of subjects per gender in each group will be calculated taking into account previous results (Cranage et al. 2008), where the difference (d) observed between protected and non-protected animals was at least of 0.9 log units, and the SD (s) was 0.5 log units. Using the equation: n = 1 + 2C(s/d)2, where C is a constant derived from the desired $p<0.05$ (**α**) and power of 0.8 (**β**), this gives a group size (n) of 5.8; hence, 6 men and 6 women will be used in each group for dosing.

10.2 Randomisation

Individuals will be randomized into one of 6 groups 1:1:1:1:1:1

Analysis

All data will be inputted using a MedSciNet e-CRF and analysed at the end of the study. Data analysis of eCRF data will be carried out Vanessa Tierney at St. Stephen's AIDS Trust.

Results from Raltegravir and Raltegravir/lamivudine will be compared at study completion. All eligible participants who receive at least two tissue biopsy visits will be included in the final data analysis. The analysis plan for estimating the pharmacodynamic dose-response curves will follow the methodology described in [O'Quigley Stats Med 2011]. In addition, the relationship between pharmacokinetic parameters (concentrations of Raltegravir and lamivudine in rectal tissue, vaginal tissue and plasma) and pharmacodynamic outcomes will be evaluated. All PK lab analysis will be conducted by the lab team at University of Liverpool and PD analysis will be conducted by the lab team at Imperial College London.

Once analysis is complete, any residual samples will be transferred to the KCL Infectious Disease Biobank for use in future ethically approved studies.

Demographic and Safety parameters

All demographic (age, height, weight, BMI, ethnic origin, etc) and clinical (physical examination, medical history, concomitant diseases) characteristics will be tabulated and analysed descriptively.

Pharmacokinetic parameters

Summary statistics of drug levels will be presented with either means with SD indicating source of inter participant variability where data are found to be parametric, or medians with IQR where data are found to be non-parametric.

Plots of the concentration time curves will be produced for plasma, genital tract and rectal compartments. Area under the concentration-time curve (AUC), maximum plasma concentration (Cmax), time to Cmax (Tmax), minimum plasma concentration (Cmin) and plasma half-life (t½) will be derived. All pharmacokinetic parameters will be presented using descriptive summary statistics including geometric mean, median, coefficient of variation and interquartile range.

Inter participant variability in plasma concentration following drug administration will be assessed by measuring the coefficient of variation (CV = SD/mean*100).

Pharmacodynamic parameters

Protection from HIV is defined as a descending viral replication curve during tissue culture resulting in complete protection from infection at day 15 following *ex vivo* HIV challenge. 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 By using a pharmacodynamic model we will determine whether Raltegravir or Raltegravir/lamivudine may options for PrEP.

Criteria for termination of the trial

The Sponsor or Investigator may terminate either part of, or the entire trial for safety or administrative reasons. A written statement fully documenting the reasons for such a termination will be provided to the Ethics Committee and the Regulatory Authority as appropriate.

11 Trial Steering Committee (TSC)

A trial steering committee is not required in view of the study protocol. Sponsors and investigators will meet on a regular basis to review recruitment and safety.

12 Data Monitoring Committee

There is not a data monitoring committee for this study. However the sponsor and investigators will meet on a regular basis to review recruitment and safety.

13 Direct Access to Source Data and Documents

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (eg patients' case sheets, blood test reports, X-ray reports, histology reports etc).

14 Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents will be submitted for review to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

The Chief Investigator will submit a final report at the conclusion of the trial to the KHP-CTO (on behalf of the Sponsor), the REC and the MHRA within the timelines defined in the Regulations.

15 Quality Assurance

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained, by the KHP Clinical Trials Office Quality Team.

16 Data Handling

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:

Patient data will be anonymised

All anonymised data will be stored on a password protected computer. All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the KHP Clinical Trials Office archiving SOP.

17 Data Management

All trial data will be inputted using MedSciNet e-CRF and stored on a database to be analysed at the end of the study. All lab data will be generated, stored and analysed by University of Liverpool and Imperial University.

18 Publication Policy

A whole or part of this trial results will be communicated, orally presented, and/or published in appropriate scientific journals. Full anonymity of participant's details will be maintained throughout. Participants wanting to see the results of the trial can request a copy of the article from the investigators once it has been published.

19 Insurance / Indemnity

Insurance for this trial will be undertaken by Guy's &St. Thomas' Hospital NHS Foundation Trust under the CNST (Clinical Negligence for Trusts) scheme.

20 Financial Aspects

Funding to conduct the trial is provided by Merck.

21 Signatures

_____ _____

Chief Investigator Date

Print name

References

1 FDA; http://www.gilead.com/pr_1660616

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3 Garcia-Lerma, J.G et al; http://www.ncbi.nlm.nih.gov/pubmed/18254653

4 Herrera, C. et al; http://www.ncbi.nlm.nih.gov/pubmed/21811139

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6 O'Quigley J and Zohar S. http://www.ncbi.nlm.nih.gov/pubmed/16434987

7 Cranage et al. 2008