



Clinical trial results:

Pre-exposure Option for reducing HIV in the UK: an open-label randomisation to immediate or Deferred daily Truvada for HIV negative gay men

Summary

EudraCT number	2012-002373-56
Trial protocol	GB
Global end of trial date	28 October 2016

Results information

Result version number	v1 (current)
This version publication date	23 December 2017
First version publication date	23 December 2017
Summary attachment (see zip file)	PROUD_Lancet_2015 (PROUDmainpaper_Lancet.pdf)

Trial information

Trial identification

Sponsor protocol code	PROUD
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Additional study identifiers

ISRCTN number	ISRCTN94465371
ClinicalTrials.gov id (NCT number)	NCT02065986
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical Research Council
Sponsor organisation address	2nd Floor, David Phillips Building, Polaris House, North Star Avenue, Swindon, United Kingdom, SN2 1FL
Public contact	PROUD trial team, Medical Research Council Clinical Trials Unit at UCL, +44 02076704783, proud.mrcctu@ucl.ac.uk
Scientific contact	PROUD trial team, Medical Research Council Clinical Trials Unit at UCL, +44 02076704783, proud.mrcctu@ucl.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 June 2015
Global end of trial reached?	Yes
Global end of trial date	28 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this pilot is to determine whether it is feasible to conduct a large trial in the UK to determine whether the immediate inclusion of anti-retroviral pre-exposure prophylaxis (PrEP) as part of the HIV risk reduction package for men who have sex with men is clinically effective and cost-effective in reducing the risk of acquiring HIV.

Protection of trial subjects:

The protocol was amended to accommodate and implement the IDMC and Trial Steering Committee recommendation in October 2014, namely that daily oral Truvada be offered to all participants in the PROUD pilot study as soon as possible and continued through to the end of the study. The recommendation was made primarily on the basis of safety, and was based on a significant and potentially preventable risk of HIV infection in the deferred group compared to the immediate group.

Note: Follow-up was scheduled to end in May 2016 but continued to Oct 2016 in order to provide PrEP to participants that still needed it.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 November 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 544
Worldwide total number of subjects	544
EEA total number of subjects	544

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	538
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment ran between November 29, 2012 and continued until April 30, 2014 in 13 sexual health clinics in England

Pre-assignment

Screening details:

Eligibility criteria: male at birth, 18 years or older, previously attended enrolling clinic, screened for HIV and other sexually transmitted infections, HIV negative by routinely used assay in previous 4 weeks or on day of enrolment, reported anal intercourse without a condom in the previous 90 days and likely to occur again in next 90 days.

Period 1

Period 1 title	Deferred phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Immediate

Arm description:

Participants received prescription of PrEP at randomisation

Arm type	Experimental
Investigational medicinal product name	Truvada
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Fixed dose combination of 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300 mg of tenofovir disoproxil fumarate or 136 mg of tenofovir) once daily

Arm title	Deferred
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Arm description:

Deferred PrEP initiation until week 48 or 13 October 2014, whichever was earliest.

Note: The deferred period was originally planned to last for 12 months. The change reflects the IDMC and TSC recommendation to offer all participants PrEP in October 2014.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Immediate	Deferred
Started	275	269
Completed	247	235
Not completed	28	34
Adverse event, serious fatal	1	-
Consent withdrawn by subject	3	4

HIV infection at baseline	2	1
Lost to follow-up	22	29

Baseline characteristics

Reporting groups

Reporting group title	Immediate
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Reporting group description:

Participants received prescription of PrEP at randomisation

Reporting group title	Deferred
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Reporting group description:

Deferred PrEP initiation until week 48 or 13 October 2014, whichever was earliest.

Note: The deferred period was originally planned to last for 12 months. The change reflects the IDMC and TSC recommendation to offer all participants PrEP in October 2014.

Reporting group values	Immediate	Deferred	Total
Number of subjects	275	269	544
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	271	267	538
From 65-84 years	4	2	6
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	272	265	537
Missing	3	4	7
Employment status			
Units: Subjects			
Employed	249	245	494
Unemployed	24	20	44
Missing	2	4	6
Education status			
Units: Subjects			
University degree	161	166	327
No University degree	111	101	212
Missing	3	2	5
Country of birth			
Units: Subjects			
UK	162	160	322
Outside of UK	110	107	217
Missing	3	2	5
Relationship status			
Units: Subjects			

Partner, living together	87	73	160
Partner, living separately	40	46	86
No partner	146	147	293
Missing	2	3	5
Circumcision status			
Units: Subjects			
Circumcised	77	79	156
Not circumcised	194	186	380
Missing	4	4	8
Chemsex in past 90 days			
Use of either γ -hydroxybutyrate, 4-methylmethcathinone, or methamphetamine to facilitate or enhance sex			
Units: Subjects			
Yes	115	116	231
No	151	143	294
Missing	9	10	19
Used post-exposure prophylaxis in past 12 months			
Units: Subjects			
Yes	91	93	184
No	167	159	326
Missing	17	17	34
Ethnicity			
Units: Subjects			
White	220	219	439
Asian	14	15	29
Black	11	10	21
Other	28	21	49
Missing	2	4	6
Any STI diagnosed in past 12 months			
Units: Subjects			
Yes	164	167	331
No	98	92	190
Missing	13	10	23
Bacterial STI diagnosed in the past 12 months			
Units: Subjects			
Yes	150	155	305
No	112	104	216
Missing	13	10	23
Rectal gonorrhoea or chlamydia diagnosed in past 12 months			
Units: Subjects			
Yes	89	83	172
No	173	176	349
Missing	13	10	23
HIV tests in past 12 months			
Units: Number			
median	3	3	
inter-quartile range (Q1-Q3)	2 to 4	2 to 4	-

End points

End points reporting groups

Reporting group title	Immediate
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Reporting group description:

Participants received prescription of PrEP at randomisation

Reporting group title	Deferred
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Reporting group description:

Deferred PrEP initiation until week 48 or 13 October 2014, whichever was earliest.

Note: The deferred period was originally planned to last for 12 months. The change reflects the IDMC and TSC recommendation to offer all participants PrEP in October 2014.

Primary: HIV infections

End point title	HIV infections
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End point description:

Compare HIV infections between trial arms during the deferred phase

End point type	Primary
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End point timeframe:

Deferred phase

End point values	Immediate	Deferred		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	235		
Units: Rate per 100PY				
number (confidence interval 90%)	1.2 (0.4 to 2.9)	9.0 (6.1 to 12.8)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Immediate v Deferred
Number of subjects included in analysis	482
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Exact Poisson regression
Parameter estimate	Rate ratio (RR)
Point estimate	7.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	2.8
upper limit	23.3

Secondary: Bacterial sexually transmitted infections

End point title	Bacterial sexually transmitted infections
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End point description:

Compare rates of STIs between trial arms during the deferred phase

End point type	Secondary
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End point timeframe:

During the deferred phase

End point values	Immediate	Deferred		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	247		
Units: No. of infections				
Any	152	124		
Gonorrhoea	103	89		
Chlamydia	77	54		
Syphilis	30	22		
Rectal gonorrhoea or chlamydia	93	77		

Statistical analyses

Statistical analysis title	Comparison of any bacterial STI
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Statistical analysis description:

Comparing proportion with STI using logistic regression, adjusting for number of screens

Comparison groups	Immediate v Deferred
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Number of subjects included in analysis	512
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Analysis specification	Pre-specified
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Analysis type	other
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P-value	= 0.74
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Method	Regression, Logistic
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Parameter estimate	Odds ratio (OR)
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Point estimate	1.07
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Confidence interval

level	90 %
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sides	2-sided
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lower limit	0.78
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upper limit	1.48
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Statistical analysis title	Comparison of gonorrhoea
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Statistical analysis description:

Comparing proportion with STI using logistic regression, adjusting for number of screens

Comparison groups	Deferred v Immediate
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.46
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.86
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.62
upper limit	1.2

Statistical analysis title	Comparison of chlamydia
Statistical analysis description:	
Comparing proportion with STI using logistic regression, adjusting for number of screens	
Comparison groups	Deferred v Immediate
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.27
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.27
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.89
upper limit	1.8

Statistical analysis title	Comparison of syphilis
Statistical analysis description:	
Comparing proportion with STI using logistic regression, adjusting for number of screens	
Comparison groups	Immediate v Deferred
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.39
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.29

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.79
upper limit	2.1

Statistical analysis title	Comparison of rectal gonorrhoea or chlamydia
Statistical analysis description:	
Comparing proportion with STI using logistic regression, adjusting for number of screens	
Comparison groups	Deferred v Immediate
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.99
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.72
upper limit	1.38

Secondary: Sexual behaviour

End point title	Sexual behaviour
End point description:	
Compare the sexual behaviour between trial arms during the deferred phase	
End point type	Secondary
End point timeframe:	
Deferred phase	

End point values	Immediate	Deferred		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	193		
Units: Participants				
0 partners	41	42		
1 partner	46	51		
2-4 partners	49	51		
5-9 partners	30	25		
10-19 partners	26	13		
20+ partners	18	11		

Statistical analyses

Statistical analysis title	Comparison of change in sexual behaviour
Statistical analysis description: Change in number of receptive anal intercourse partners without a partner from baseline to the end of the deferred phase	
Comparison groups	Immediate v Deferred
Number of subjects included in analysis	403
Analysis specification	Post-hoc
Analysis type	other ^[1]
P-value	= 0.03
Method	Regression, Linear

Notes:

[1] - Linear regression (for category number) adjusting for number of partners at baseline

Secondary: PrEP prescription

End point title	PrEP prescription ^[2]
End point description: The mean percentage of days covered by prescription of study drug	
End point type	Secondary
End point timeframe: Deferred phase	

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This is not a relevant outcome for the deferred arm since they did not have access to study drug during this period

End point values	Immediate			
Subject group type	Reporting group			
Number of subjects analysed	275			
Units: Percentage				
arithmetic mean (standard deviation)	0.88 (± 0.25)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs - randomisation to end of the trial

AEs - randomisation to end of deferred phase in ppts in immediate group who interrupted/stopped treatment

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Participants
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Reporting group description:

pooled over study arms

Serious adverse events	Participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	85 / 544 (15.63%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colorectal cancer			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Surgical and medical procedures			
Surgery			

subjects affected / exposed	2 / 544 (0.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abscess drainage			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc operation			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Removal of internal fixation			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tendon operation			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Liver transplant			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	2 / 544 (0.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Social circumstances			
Physical assault			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast			

disorders			
Epididymitis			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Orchitis			
subjects affected / exposed	2 / 544 (0.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Priapism			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Testicular swelling			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Testicular torsion			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chest pain			
subjects affected / exposed	2 / 544 (0.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 544 (0.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		

Sinusitis			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug withdrawal syndrome			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Panic attack			
subjects affected / exposed	2 / 544 (0.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	2 / 544 (0.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	4 / 544 (0.74%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder			
subjects affected / exposed	2 / 544 (0.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			

Liver function test abnormal subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Accidental poisoning			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	5 / 544 (0.92%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Post procedural haematuria			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Substance-induced psychotic disorder			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	2 / 544 (0.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 544 (0.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Anal abscess			
subjects affected / exposed	2 / 544 (0.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	3 / 544 (0.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			

subjects affected / exposed	3 / 544 (0.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Food poisoning			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric varices haemorrhage			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis chronic			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis bacterial			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Ascites			
subjects affected / exposed	2 / 544 (0.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Biliary sepsis			

subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Cellulitis			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal pain			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Hand fracture			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Arthropathy				
subjects affected / exposed	1 / 544 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ankle fracture				
subjects affected / exposed	1 / 544 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Joint dislocation				
subjects affected / exposed	1 / 544 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	1 / 544 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	1 / 544 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple fractures				
subjects affected / exposed	1 / 544 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal fracture				
subjects affected / exposed	1 / 544 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				
subjects affected / exposed	1 / 544 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				

Acute hepatitis C				
subjects affected / exposed	3 / 544 (0.55%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Acute HIV infection				
subjects affected / exposed	2 / 544 (0.37%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	1 / 544 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea infectious				
subjects affected / exposed	1 / 544 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis bacterial				
subjects affected / exposed	1 / 544 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis shigella				
subjects affected / exposed	3 / 544 (0.55%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Injection site abscess				
subjects affected / exposed	1 / 544 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Joint abscess				
subjects affected / exposed	1 / 544 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mumps				

subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shigella infection			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 544 (3.86%)		
Investigations			
serum creatinine increased			
subjects affected / exposed ^[1]	3 / 275 (1.09%)		
occurrences (all)	3		
abnormal liver function tests			

<p>subjects affected / exposed^[2]</p> <p>occurrences (all)</p>	<p>1 / 275 (0.36%)</p> <p>1</p>		
<p>Injury, poisoning and procedural complications</p> <p>Fall</p> <p>subjects affected / exposed^[3]</p> <p>occurrences (all)</p>	<p>1 / 275 (0.36%)</p> <p>1</p>		
<p>Nervous system disorders</p> <p>Headache</p> <p>subjects affected / exposed^[4]</p> <p>occurrences (all)</p>	<p>2 / 275 (0.73%)</p> <p>3</p>		
<p>General disorders and administration site conditions</p> <p>Flu like illness</p> <p>subjects affected / exposed^[5]</p> <p>occurrences (all)</p>	<p>1 / 275 (0.36%)</p> <p>1</p>		
<p>Gastrointestinal disorders</p> <p>Nausea</p> <p>subjects affected / exposed^[6]</p> <p>occurrences (all)</p> <p>Gastroenteritis</p> <p>subjects affected / exposed^[7]</p> <p>occurrences (all)</p>	<p>4 / 275 (1.45%)</p> <p>4</p> <p>1 / 275 (0.36%)</p> <p>1</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Chest pain</p> <p>subjects affected / exposed^[8]</p> <p>occurrences (all)</p>	<p>3 / 275 (1.09%)</p> <p>3</p>		
<p>Skin and subcutaneous tissue disorders</p> <p>Lipoatrophy</p> <p>subjects affected / exposed^[9]</p> <p>occurrences (all)</p>	<p>1 / 275 (0.36%)</p> <p>1</p>		
<p>Psychiatric disorders</p> <p>Depression</p> <p>subjects affected / exposed^[10]</p> <p>occurrences (all)</p> <p>Anxiety</p> <p>subjects affected / exposed^[11]</p> <p>occurrences (all)</p>	<p>2 / 275 (0.73%)</p> <p>2</p> <p>2 / 275 (0.73%)</p> <p>2</p>		

Manic depression subjects affected / exposed ^[12] occurrences (all)	1 / 275 (0.36%) 1		
Musculoskeletal and connective tissue disorders chest pain musculoskeletal subjects affected / exposed ^[13] occurrences (all) polyarthralgia subjects affected / exposed ^[14] occurrences (all) Arthralgia subjects affected / exposed ^[15] occurrences (all) loin pain subjects affected / exposed ^[16] occurrences (all)	1 / 275 (0.36%) 1 1 / 275 (0.36%) 1 2 / 275 (0.73%) 2 1 / 275 (0.36%) 1		
Infections and infestations Hospital acquired pneumonia subjects affected / exposed ^[17] occurrences (all)	1 / 275 (0.36%) 1		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: reporting for ppts in immediate group who interrupted/stopped treatment

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: reporting for ppts in immediate group who interrupted/stopped treatment

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: reporting for ppts in immediate group who interrupted/stopped treatment

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: reporting for ppts in immediate group who interrupted/stopped treatment

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: reporting for ppts in immediate group who interrupted/stopped treatment

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: reporting for ppts in immediate group who interrupted/stopped treatment

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: reporting for ppts in immediate group who interrupted/stopped treatment

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: reporting for ppts in immediate group who interrupted/stopped treatment

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: reporting for ppts in immediate group who interrupted/stopped treatment

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: reporting for ppts in immediate group who interrupted/stopped treatment

[11] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: reporting for ppts in immediate group who interrupted/stopped treatment

[12] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: reporting for ppts in immediate group who interrupted/stopped treatment

[13] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: reporting for ppts in immediate group who interrupted/stopped treatment

[14] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: reporting for ppts in immediate group who interrupted/stopped treatment

[15] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: reporting for ppts in immediate group who interrupted/stopped treatment

[16] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: reporting for ppts in immediate group who interrupted/stopped treatment

[17] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: reporting for ppts in immediate group who interrupted/stopped treatment

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 February 2013	Update to CTA - clarification that Truvada of primary use in the study is Gilead clinical trial stock. Commercial stock details added as use in emergency if clinical need
19 September 2013	The update provided updated relevant results, clarified that the recruitment strategies would be broader than clinics and that follow-up data could be collected within the GUM clinic network as this is more convenient for the participants and provided additional detail on the quantitative and qualitative data collection. Section 5 was been updated as it may have been necessary to post drugs. Further details were provided about one to one and group discussions and included the related PIS, IC and one to one interview guide. The Investigators wished to clarify that discontinuation of Truvada is only a Serious Adverse Event when the clinician decided they would never prescribe Truvada again (section 7), and that soundex would be needed in addition to date of birth to cross-check the PHE database for HIV endpoints (section 8). In line with MRC CTU and international guidelines, we have expanded the oversight to include Participant Involvement meetings, and clarified the independent data monitoring that we have implemented on the recommendation of the Trial Steering Committee (section 14).
17 October 2014	Protocol 1.3 - The protocol was amended to accommodate and implement the Trial Steering Committee recommendation of 9th October 2014, namely that daily oral Truvada be offered to all participants in the PROUD pilot study as soon as possible and continued through to the end of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26364263>