Clinical trial results:
Be-PrEP-ared: HIV prevention with Pre-exposure prophylaxis – a demonstration project in high risk men having sex with men in Belgium

Summary

EudraCT number	2015-000054-37
Trial protocol	BE
Global end of trial date	16 May 2018

Results information

Result version number	v1 (current)
This version publication date	07 September 2019
First version publication date	07 September 2019

Trial information

Trial identification

Sponsor protocol code	ITM0514

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Institute of Tropical Medicine Antwerp
Sponsor organisation address	Nationalestraat 155, Antwerp, Belgium, 2000
Public contact	Clinical Trials Unit, Institute of Tropical Medicine, 0032 33455557, yvanherrewege@itg.be
Scientific contact	Clinical Trials Unit, Institute of Tropical Medicine, 0032 33455557, yvanherrewege@itg.be

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	23 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 May 2018
Global end of trial reached?	Yes
Global end of trial date	16 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Among MSM at high risk for acquiring HIV:
- To document their current preventive needs, including the uptake, acceptability and feasibility of using PrEP intermittently or daily
- To evaluate adherence to two different PrEP regimens

Protection of trial subjects:

- EC approval
- No fault insurance
- Pseudonymisation of the trial data
- Behavioral counseling

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 200
Worldwide total number of subjects	200
EEA total number of subjects	200

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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	198
From 65 to 84 years	2

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

FPFV: 30/Sep/2015
FPLV: 16/May/2018
Screened: 219
Enrolled: 200

Pre-assignment

Screening details:

219 subjects screened and 200 enrolled. Most common reasons for not being included were that subjects did not fall under the criteria for high-risk sexual contacts.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This is an open-label study and participants will decide for themselves if they want to use PrEP or not. When using PrEP they can self-select in which arm to be enrolled, thus between two regimens (daily or event-driven).

Arms

Are arms mutually exclusive?	No
Arm title	Daily

Arm description:

Participants take on tablet of PrEP on a daily basis.

Arm type	Daily use
Investigational medicinal product name	Truvada
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet a day. PrEP intake should be every 24 hours ± 2 hours (with a window period of two hours before or after the scheduled time). The scheduled time of tablet intake should remain the same every day. When starting PrEP, the participant should not have unsafe sex until he took 2 pills before the first sexual act (with the second pill at least 2h before sex).

Arm title	Event-driven

Arm description:

Participant takes PrEP around the time of sexual contact.

Arm type	Event-driven use
Investigational medicinal product name	Truvada
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A dose of two pills 2-24 hours before the sex-act, and one tablet of Truvada every 24 hours (starting when the first two tablets are taken) during the whole period of sexual activity including two doses after the last sexual intercourse. The tablets should be taken every 24 hours + 2 hours (with a window period of two hours before or after the scheduled time).

Number of subjects in period 1	Daily	Event-driven
Started	153	47
Completed	153	47

Baseline characteristics

Reporting groups	
Reporting group title	Daily
Reporting group description:	
Participants take on tablet of PrEP on a daily basis.	
Reporting group title	Event-driven
Reporting group description:	
Participant takes PrEP around the time of sexual contact.	

Reporting group values	Daily	Event-driven	Total
Number of subjects	153	47	200
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)	152	46	198
From 65-84 years	1	1	2
85 years and over	0	0	0
Age continuous			
Units: years			
median	38	39	
inter-quartile range (Q1-Q3)	31 to 43	34 to 47	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	153	47	200
Height			
Units: cm			
median	180	181	
inter-quartile range (Q1-Q3)	176 to 186	177 to 186	-
Weight			
Units: kilogram(s)			
median	78	75.7	
inter-quartile range (Q1-Q3)	71 to 84	69 to 85	-
Systolic blood pressure			
Units: mmHg			
median	129	128	
inter-quartile range (Q1-Q3)	119 to 137	117 to 140	-
Diastolic blood pressure			
Units: mmHg			
median	85	83	
inter-quartile range (Q1-Q3)	79 to 92	75 to 93	-

Subject analysis sets

Subject analysis set title	All enrolled participants
Subject analysis set type	Full analysis

Subject analysis set description:

All enrolled participants, independent of study arm

Reporting group values	All enrolled participants		
Number of subjects	200		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	198		
From 65-84 years	2		
85 years and over	0		
Age continuous			
Units: years			
median			
inter-quartile range (Q1-Q3)			
Gender categorical			
Units: Subjects			
Female	0		
Male	200		
Height			
Units: cm			
median			
inter-quartile range (Q1-Q3)			
Weight			
Units: kilogram(s)			
median			
inter-quartile range (Q1-Q3)			
Systolic blood pressure			
Units: mmHg			
median			
inter-quartile range (Q1-Q3)			
Diastolic blood pressure			
Units: mmHg			
median			
inter-quartile range (Q1-Q3)			

End points

End points reporting groups

Reporting group title	Daily
Reporting group description:	
Participants take on tablet of PrEP on a daily basis.	
Reporting group title	Event-driven
Reporting group description:	
Participant takes PrEP around the time of sexual contact.	
Subject analysis set title	All enrolled participants
Subject analysis set type	Full analysis
Subject analysis set description:	
All enrolled participants, independent of study arm	

Primary: Unsafe sex behavior

End point title	Unsafe sex behavior[1]
End point description:	
Unsafe sex behavior is defined as condomless anal intercourse in the last three months with a casual partner with unknown HIV status or HIV positive status.	
End point type	Primary
End point timeframe:	
Screening	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No comparison between both arms was done.

End point values	Daily	Event-driven		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	47		
Units: Participants	89	18		

Statistical analyses

No statistical analyses for this end point

Primary: Intention to use PrEP

End point title	Intention to use PrEP[2]
End point description:	
The proportion of participants who have the intention to use PrEP in the future.	
End point type	Primary
End point timeframe:	
Screening	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No comparison between both arms was done.

End point values	All enrolled participants			
Subject group type	Subject analysis set			
Number of subjects analysed	104			
Units: Participants	100			

Statistical analyses

No statistical analyses for this end point

Primary: Retention rate: discontinuation

End point title	Retention rate: discontinuation[3]

End point description:

The incidence rate of (first) discontinuation of PrEP.

End point type	Primary

End point timeframe:

Whole study

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No comparison between both arms was done.

End point values	Daily	Event-driven		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	47		
Units: Incidence rate per person-year				
number (confidence interval 95%)	0.30 (0.23 to 0.39)	0.25 (0.15 to 0.41)		

Statistical analyses

No statistical analyses for this end point

Primary: Incidence rate: restarting

End point title	Incidence rate: restarting[4]

End point description:

The incidence rate of restarting PrEP after (first) discontinuation.

End point type	Primary

End point timeframe:

Whole study

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No comparison between both arms was done.

End point values	Daily	Event-driven		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	47		
Units: Incidence rate per person-year				
number (confidence interval 95%)	10.61 (8.09 to 13.92)	4.19 (2.38 to 7.39)		

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of covered sex days

End point title	Proportion of covered sex days

End point description:

Adherence is calculated as the proportion of days with anal sex acts that are covered by PrEP intake

End point type	Primary

End point timeframe:

Whole study

End point values	Daily	Event-driven		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	47		
Units: Proportion of days (%)				
number (confidence interval 95%)	96.5 (96.3 to 96.8)	67 (65.4 to 68.5)		

Statistical analyses

Statistical analysis title	Comparison of adherence between arms
Comparison groups	Daily v Event-driven
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis

Primary: Drug levels: Month 1

End point title	Drug levels: Month 1

End point description:

At least 10 ng of tenofovir per milliliter in plasma is considered evidence that TDF has been taken within the previous 48 hours.

End point type	Primary

End point timeframe:

Month 1

End point values	Daily	Event-driven		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	44		
Units: Participants	143	24		

Statistical analyses

Statistical analysis title	Comparison of drug levels at month 1 between arms
Comparison groups	Daily v Event-driven
Number of subjects included in analysis	194
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis

Primary: Drug levels: Month 3

End point title	Drug levels: Month 3

End point description:

At least 10 ng of tenofovir per milliliter in plasma is considered evidence that TDF has been taken within the previous 48 hours.

End point type	Primary

End point timeframe:

Month 3

End point values	Daily	Event-driven		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146	47		
Units: Participants	140	24		

Statistical analyses

Statistical analysis title	Comparison of drug levels at month 3 between arms
Comparison groups	Daily v Event-driven

Number of subjects included in analysis	193
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis

Secondary: HIV seroconversion

End point title	HIV seroconversion

End point description:

HIV seroconversion during the study

End point type	Secondary

End point timeframe:

Whole study

End point values	All enrolled participants			
Subject group type	Subject analysis set			
Number of subjects analysed	200			
Units: Participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Accepting HIV testing using oral fluid self-sampling testing

End point title	Accepting HIV testing using oral fluid self-sampling testing

End point description:

The proportions of participants who prefers oral fluid self-sampling above blood sampling for HIV testing.

End point type	Secondary

End point timeframe:

Whole study

End point values	All enrolled participants			
Subject group type	Subject analysis set			
Number of subjects analysed	104			
Units: Participants	45			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline visit until final study visit.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Daily
Reporting group description: -	
Reporting group title	Event-driven
Reporting group description: -	

Serious adverse events	Daily	Event-driven	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 153 (6.54%)	7 / 47 (14.89%)	
number of deaths (all causes)	0	3	
number of deaths resulting from adverse events	0	3	
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	0 / 153 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Overdose			
subjects affected / exposed	1 / 153 (0.65%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 153 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Drug rehabilitation			

subjects affected / exposed	1 / 153 (0.65%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 153 (0.65%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	1 / 153 (0.65%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Priapism			
subjects affected / exposed	1 / 153 (0.65%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asphyxia			
subjects affected / exposed	0 / 153 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 153 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Depression			
subjects affected / exposed	0 / 153 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Personality disorder			

subjects affected / exposed	1 / 153 (0.65%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric decompensation			
subjects affected / exposed	0 / 153 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 153 (0.65%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Dysentery			
subjects affected / exposed	0 / 153 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis A			
subjects affected / exposed	1 / 153 (0.65%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis bacterial			
subjects affected / exposed	1 / 153 (0.65%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural empyema			
subjects affected / exposed	1 / 153 (0.65%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Daily	Event-driven	
Total subjects affected by non-serious adverse events subjects affected / exposed	151 / 153 (98.69%)	45 / 47 (95.74%)	
Investigations Chlamydia test positive subjects affected / exposed occurrences (all)	61 / 153 (39.87%) 61	13 / 47 (27.66%) 13	
Herpes simplex test positive subjects affected / exposed occurrences (all)	13 / 153 (8.50%) 13	3 / 47 (6.38%) 3	
Mycoplasma test positive subjects affected / exposed occurrences (all)	44 / 153 (28.76%) 44	13 / 47 (27.66%) 13	
Neisseria test positive subjects affected / exposed occurrences (all)	65 / 153 (42.48%) 65	14 / 47 (29.79%) 14	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	5 / 153 (3.27%) 5	5 / 47 (10.64%) 5	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	22 / 153 (14.38%) 22	5 / 47 (10.64%) 5	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	24 / 153 (15.69%) 24	7 / 47 (14.89%) 7	
Influenza like illness subjects affected / exposed occurrences (all)	9 / 153 (5.88%) 9	4 / 47 (8.51%) 4	

Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	14 / 153 (9.15%)	3 / 47 (6.38%)	
occurrences (all)	14	3	
Abdominal pain			
subjects affected / exposed	15 / 153 (9.80%)	3 / 47 (6.38%)	
occurrences (all)	15	3	
Diarrhoea			
subjects affected / exposed	50 / 153 (32.68%)	12 / 47 (25.53%)	
occurrences (all)	50	12	
Epigastric discomfort			
subjects affected / exposed	8 / 153 (5.23%)	5 / 47 (10.64%)	
occurrences (all)	8	5	
Flatulence			
subjects affected / exposed	22 / 153 (14.38%)	5 / 47 (10.64%)	
occurrences (all)	22	5	
Nausea			
subjects affected / exposed	15 / 153 (9.80%)	5 / 47 (10.64%)	
occurrences (all)	15	5	
Proctitis			
subjects affected / exposed	9 / 153 (5.88%)	4 / 47 (8.51%)	
occurrences (all)	9	4	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	8 / 153 (5.23%)	4 / 47 (8.51%)	
occurrences (all)	8	4	
Psychiatric disorders			
Depression			
subjects affected / exposed	7 / 153 (4.58%)	5 / 47 (10.64%)	
occurrences (all)	7	5	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	22 / 153 (14.38%)	4 / 47 (8.51%)	
occurrences (all)	22	4	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	15 / 153 (9.80%)	2 / 47 (4.26%)	
occurrences (all)	15	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	8 / 153 (5.23%)	5 / 47 (10.64%)	
occurrences (all)	8	5	
Gastroenteritis			
subjects affected / exposed	13 / 153 (8.50%)	1 / 47 (2.13%)	
occurrences (all)	13	1	
Influenza			
subjects affected / exposed	7 / 153 (4.58%)	5 / 47 (10.64%)	
occurrences (all)	7	5	
Lymphogranuloma venereum			
subjects affected / exposed	14 / 153 (9.15%)	0 / 47 (0.00%)	
occurrences (all)	14	0	
Pharyngitis			
subjects affected / exposed	16 / 153 (10.46%)	9 / 47 (19.15%)	
occurrences (all)	16	9	
Proctitis gonococcal			
subjects affected / exposed	13 / 153 (8.50%)	6 / 47 (12.77%)	
occurrences (all)	13	6	
Syphilis			
subjects affected / exposed	27 / 153 (17.65%)	5 / 47 (10.64%)	
occurrences (all)	27	5	
Urethritis			
subjects affected / exposed	14 / 153 (9.15%)	1 / 47 (2.13%)	
occurrences (all)	14	1	
Urethritis chlamydial			
subjects affected / exposed	9 / 153 (5.88%)	6 / 47 (12.77%)	
occurrences (all)	9	6	
Urethritis gonococcal			
subjects affected / exposed	20 / 153 (13.07%)	2 / 47 (4.26%)	
occurrences (all)	20	2	
Viral upper respiratory tract infection			

subjects affected / exposed occurrences (all)	40 / 153 (26.14%) 40	11 / 47 (23.40%) 11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 December 2016	Extension of the open label Be-PrEP-ared cohort study with 3-monthly follow-up visits until the end of Jan 2018 for early participants (M18 scheduled before 01/11/2017). This proposition is guided by ethical considerations (extended support to HIV prevention for current trial participants during the window period) and scientific added value (longer follow up allows to collect more valuable info on primary and secondary endpoints). The supply of Truvada as original foreseen for the Be-PrEP-ared study is sufficient to cover also the prolonged participation of those study subjects which would roll out of the study before end of 2017, and the manufacturer of Truvada (Gilead) gave its permission to use the drug as such.
11 December 2017	An interim analysis was performed on het collected study data of the first 12 months of enrollment for all participants. - Number and % participants who switch regimen (from daily to event-driven of inverse) - Incidence Neisseria gonorrhoeae, Chlamydia trachomatis, Mycoplasma genitalium, Trichomonas vaginalis, syphilis, Hepatitis C: cumulative over 12 months; per PrEP regimen - HIV seroconversion rate - Proportion of covered sex acts: per 3 months, per regimen and per risk category (low or high risk) - Self-perceived skills to adhere - Reported total number of sex partners (ano + occasion + steady), per 3 months and per regimen - Reported number of anonymous partners, per 3 months and per PrEP regimen - Reported number of casual partners, per 3 months and per PrEP regimen - Reported proportion of sexual partners with whom condom was used for receptive, top and receptive/top anal intercourse, per 3 months, per type partner and per PrEP regimen - Reported number of sex under influence of alcohol and/or drugs, per 9 months and per PrEP regimen In addition, the baseline characteristics, as described in chapter 12.1.2.2. will be included in the interim analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported