Clinical trial results:
A randomised controlled trial of a strategy of switching to boosted protease inhibitor monotherapy versus continuing combination antiretroviral therapy for the long-term management of HIV-1 infected patients who have achieved sustained virological suppression on highly-active antiretroviral therapy

Summary

EudraCT number	2007-006448-23
Trial protocol	GB
Global end of trial date	31 December 2018

Results information

Result version number	v1 (current)
This version publication date	15 January 2020
First version publication date	15 January 2020

Trial information

Trial identification

Sponsor protocol code	PIVOT

Additional study identifiers

ISRCTN number	ISRCTN04857074
ClinicalTrials.gov id (NCT number)	NCT01230580
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical Research Council
Sponsor organisation address	90 High Holborn, London, United Kingdom, WC1V 6LJ
Public contact	Wolfgang Stohr, MRC Clinical Trials Unit at UCL Institute of Clinical Trials & Methodology , 44 02706704800, w.stohr@ucl.ac.uk
Scientific contact	Wolfgang Stohr, MRC Clinical Trials Unit at UCL Institute of Clinical Trials & Methodology , 44 02706704800, w.stohr@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	16 December 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 November 2013
Global end of trial reached?	Yes
Global end of trial date	31 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether a strategy of switching to PI monotherapy is as good as continuing triple drug therapy (the standard of care) in terms of the proportion of patients who maintain all possible drug treatment options after at least 3 years of follow-up.

Protection of trial subjects:

Inclusion/exclusion criteria and follow-up examinations were carefully chosen to minimise the risk of trial subjects. For example, to minimise the risk of myocardial infarction in patients exposed to PI treatment, PIVOT included formal assessment of cardiovascular risk as part of the screening criteria, and did not enrol patients with very high level of background risk. Lipid levels were measured periodically, and clinicians were encouraged to manage lipid elevations fastidiously according to current guidelines. The protocol also allowed switching to other PIs with smaller effects on lipids.
The PIs used in the trial were all licensed drugs which had been used in many thousands of patients. Therefore risk of adverse events was known to be relatively small. Furthermore, the inclusion/exclusion criteria prevented patients at risk of metabolic problems and more serious side effects to enter the trial. Physicians and patients were allowed to select the PI best suited to that patient, and, if necessary, to switch to an alternative PI if there were tolerability or toxicity problems. Patients were monitored carefully during the intervention for side effects of PIs allowing appropriate management of these effects. Lastly, the protocol allowed switch back to triple-therapy in the event of unmanageable toxicity occurring in the PI monotherapy arm.
To minimise the risk of virological failure with development of resistance, patients had to be stable on their current standard-of-care regimen, with a relatively low probability of treatment failure in the long-term. In order to minimise the risk of developing resistance, patients who were known to have resistance to PIs or who had any evidence of failure on a PI-containing regimen were excluded. Furthermore, patients will be monitored closely in the initial three months after treatment switch with regular VL testing, and patients who did not maintain virological suppression were switched back promptly to triple-therapy.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 587
Worldwide total number of subjects	587
EEA total number of subjects	587

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)	575
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	695[1]
Number of subjects completed	587

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not return after screening: 19
Reason: Number of subjects	VL >=50 cop/mL at screening or previous 24 weeks: 25
Reason: Number of subjects	previous ART change due to unsatisfactory VL: 26
Reason: Number of subjects	not on two NRTIs and one NNRTI or PI regimen: 7
Reason: Number of subjects	Other reason: 25
Reason: Number of subjects	Multiple reasons: 6

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same. Justification: 108 patients were screened but were not enrolled due to ineligibility or because they did not return after screening.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ongoing triple therapy

Arm description:

Patients randomised to the control arm will continue to take their standard-of-care triple-therapy regimen. Changes of therapy can be made for virological failure or drug-related toxicity as clinically indicated, but patients will be expected to remain on the strategy of receiving standard-of-care triple-therapy for the duration of the trial. The choice of drugs for use in the triple-therapy strategy is left to the discretion of the physician and patient.

Arm type	Active comparator
Investigational medicinal product name	tenofovir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

245 mg once daily

Investigational medicinal product name	emtricitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details: 200 mg once daily	
Investigational medicinal product name	lamivudine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 150 mg every 12 hours, alternatively 300 mg once daily	
Investigational medicinal product name	efavirenz
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 600 mg once daily	
Investigational medicinal product name	abacavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 600 mg daily in 1–2 divided doses	
Investigational medicinal product name	darunavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 600 mg twice daily, alternatively 800 mg once daily	
Investigational medicinal product name	atazanavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 300 mg once daily	
Investigational medicinal product name	nevirapine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 200 mg once daily	
Investigational medicinal product name	lopinavir with ritonavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 400/100 mg twice daily, alternatively 800/200 mg once daily	

Investigational medicinal product name	saquinavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 1 g every 12 hours	
Investigational medicinal product name	zidovudine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 250–300 mg twice daily	
Investigational medicinal product name	rilpivirine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 25 mg once daily	
Investigational medicinal product name	raltegravir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 400 mg twice daily	
Investigational medicinal product name	etravirine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 200 mg twice daily	
Investigational medicinal product name	fosamprenavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 700 mg twice daily	
Investigational medicinal product name	maraviroc
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 300 mg twice daily	
Investigational medicinal product name	didanosine
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

400 mg daily in 1–2 divided doses

Investigational medicinal product name	ritonavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100–200 mg 1–2 times a day; Low-dose booster to increase effect of other protease inhibitors

Arm title	PI monotherapy

Arm description:

Treatment with a single ritonavir-boosted protease inhibitor (PI). PIVOT was a strategic trial and hence the choice of protease inhibitor was left to physician and patient discretion. Any licensed, ritonavir-boosted PI was permitted. Switches to alternative PIs were permitted during the trial to avoid or minimise drug-related toxicity, to minimise the risk of interactions with any necessary concomitant medication, to create a more acceptable treatment schedule, or to take account of changes in current opinion of the relative merits of protease inhibitors in this therapeutic setting.

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

Dosage and administration details:

600 mg twice daily, alternatively 800 mg once daily

Investigational medicinal product name	atazanavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

300 mg once daily

Investigational medicinal product name	lopinavir with ritonavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400/100 mg twice daily, alternatively 800/200 mg once daily

Investigational medicinal product name	saquinavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 g every 12 hours

Investigational medicinal product name	ritonavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
100–200 mg 1–2 times a day; Low-dose booster to increase effect of other protease inhibitors

Number of subjects in period 1	Ongoing triple therapy	PI monotherapy
Started	291	296
Completed	279	285
Not completed	12	11
Adverse event, serious fatal	1	6
Consent withdrawn by subject	5	2
Lost to follow-up	6	3

Baseline characteristics

Reporting groups	
Reporting group title	Ongoing triple therapy

Reporting group description:

Patients randomised to the control arm will continue to take their standard-of-care triple-therapy regimen. Changes of therapy can be made for virological failure or drug-related toxicity as clinically indicated, but patients will be expected to remain on the strategy of receiving standard-of-care triple-therapy for the duration of the trial. The choice of drugs for use in the triple-therapy strategy is left to the discretion of the physician and patient.

Reporting group title	PI monotherapy

Reporting group description:

Treatment with a single ritonavir-boosted protease inhibitor (PI). PIVOT was a strategic trial and hence the choice of protease inhibitor was left to physician and patient discretion. Any licensed, ritonavir-boosted PI was permitted. Switches to alternative PIs were permitted during the trial to avoid or minimise drug-related toxicity, to minimise the risk of interactions with any necessary concomitant medication, to create a more acceptable treatment schedule, or to take account of changes in current opinion of the relative merits of protease inhibitors in this therapeutic setting.

Reporting group values	Ongoing triple therapy	PI monotherapy	Total
Number of subjects	291	296	587
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)	283	292	575
From 65-84 years	8	4	12
85 years and over	0	0	0
Age continuous Units: years			
median	43	45	
inter-quartile range (Q1-Q3)	37 to 49	39 to 50	-
Gender categorical Units: Subjects			
Female	64	73	137
Male	227	223	450
Route of infection Units: Subjects			
Homosexual	175	176	351
Heterosexual	108	108	216
Other	8	12	20
Ethnic origin Units: Subjects			
White	206	195	401
Black	73	90	163
Other	12	11	23

Hepatitis C virus antibody status Units: Subjects			
positive	7	14	21
negative	281	282	563
unknown	3	0	3
Previous AIDS-defining illness Units: Subjects			
yes	59	57	116
no	232	239	471
Undetectable baseline HIV viral load Units: Subjects			
yes	276	279	555
no	14	17	31
missing	1	0	1
On first ART combination Units: Subjects			
yes	91	96	187
no	200	200	400
NNRTI at entry Units: Subjects			
Efavirenz	115	115	230
Nevirapine	42	39	81
Etravirine	0	3	3
none	134	139	273
Protease inhibitor at entry Units: Subjects			
Atazanavir	59	59	118
Lopinavir	28	49	77
Darunavir	24	13	37
Saquinavir	16	15	31
Fosamprenavir	7	3	10
none	157	157	314
NRTIs at entry Units: Subjects			
Emtricitabine and tenofovir	190	180	370
Lamivudine and abacavir	80	82	162
Other	21	34	55
Resistance test result available before trial Units: Subjects			
yes	181	165	346
no	110	131	241
Intermediate-level or high-level resistance to NRTI or NNRTI before trial Units: Subjects			
yes	4	7	11
no	287	289	576
Nadir CD4 count Units: cells per µL			
median	181	170	
inter-quartile range (Q1-Q3)	90 to 258	80 to 239	-
CD4 count			

Units: cells per µL			
median	512	516	
inter-quartile range (Q1-Q3)	386 to 658	402 to 713	-
Duration of undetectable viral load			
Units: months			
median	36	38	
inter-quartile range (Q1-Q3)	17 to 62	22 to 66	-
Years since ART started			
Units: years			
median	3.9	4.2	
inter-quartile range (Q1-Q3)	2.0 to 6.4	2.4 to 6.9	-
Number of drugs ever received			
Units: number			
median	5	4	
inter-quartile range (Q1-Q3)	3 to 6	3 to 6	-

End points

End points reporting groups

Reporting group title	Ongoing triple therapy

Reporting group description:

Patients randomised to the control arm will continue to take their standard-of-care triple-therapy regimen. Changes of therapy can be made for virological failure or drug-related toxicity as clinically indicated, but patients will be expected to remain on the strategy of receiving standard-of-care triple-therapy for the duration of the trial. The choice of drugs for use in the triple-therapy strategy is left to the discretion of the physician and patient.

Reporting group title	PI monotherapy

Reporting group description:

Treatment with a single ritonavir-boosted protease inhibitor (PI). PIVOT was a strategic trial and hence the choice of protease inhibitor was left to physician and patient discretion. Any licensed, ritonavir-boosted PI was permitted. Switches to alternative PIs were permitted during the trial to avoid or minimise drug-related toxicity, to minimise the risk of interactions with any necessary concomitant medication, to create a more acceptable treatment schedule, or to take account of changes in current opinion of the relative merits of protease inhibitors in this therapeutic setting.

Primary: Loss of future drug options

End point title	Loss of future drug options

End point description:

The primary outcome was loss of future drug options, defined as new intermediate-level or high-level resistance to one or more drugs in contemporary use to which we deemed patient's virus to be sensitive at trial entry (assessed at 3 years). We defined contemporary use on the basis of inclusion in present UK treatment guidelines, with saquinavir added because this drug was taken by some participants during the trial.

End point type	Primary

End point timeframe:

any time from randomisation to 3 years after randomisation

End point values	Ongoing triple therapy	PI monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	296		
Units: Subjects				
Reached endpoint	2	6		
Did not reach endpoint	289	290		

Statistical analyses

Statistical analysis title	Primary analysis of the primary endpoint

Statistical analysis description:

We estimated the absolute difference between groups in reduction of future drug options using Kaplan-Meier analysis, with the 95% CI (two-sided) derived with bootstrap methods. Participants were censored at the time of death, loss to follow-up, or withdrawal. This analysis and all other analyses in PIVOT were made according to the intention-to-treat principle.

Comparison groups	PI monotherapy v Ongoing triple therapy

Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Risk difference (RD)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	3.4

Notes:

[1] - We defined non-inferiority of the PI-mono group by the upper limit of the two-sided 95% CI for the difference in proportions of patients who maintain all future drug options during 3 years (OT group minus the PI-mono group) being less than 10%.

Secondary: Confirmed viral load rebound

End point title	Confirmed viral load rebound

End point description:

End point type	Secondary

End point timeframe:

Any time from randomisation to the end of follow-up

End point values	Ongoing triple therapy	PI monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	296		
Units: Subjects				
Reached endpoint	8	95		
Did not reach endpoint	283	201		

Statistical analyses

Statistical analysis title	Analysis of confirmed viral load rebound

Statistical analysis description:

The proportion of patients who had viral load rebound was estimated with Kaplan-Meier analysis and compared groups by use of a log-rank test.

Comparison groups	Ongoing triple therapy v PI monotherapy
Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Risk difference (RD)
Point estimate	31.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	24.6
upper limit	39

Secondary: Death

End point title	Death

End point description:

End point type	Secondary

End point timeframe:

From randomisation until the end of follow-up

End point values	Ongoing triple therapy	PI monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	296		
Units: Subject				
Died	1	6		
Did not die	290	290		

Statistical analyses

Statistical analysis title	Analysis of death
Comparison groups	PI monotherapy v Ongoing triple therapy
Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Fisher exact

Secondary: AIDS-defining event

End point title	AIDS-defining event

End point description:

End point type	Secondary

End point timeframe:

Any time from randomisation to the end of follow-up

End point values	Ongoing triple therapy	PI monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	296		
Units: Subjects				
Reached endpoint	1	1		
Did not reach endpoint	290	295		

Statistical analyses

Statistical analysis title	Analysis of AIDS-defining events
Comparison groups	Ongoing triple therapy v PI monotherapy
Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Secondary: Serious non-AIDS event

End point title	Serious non-AIDS event

End point description:

End point type	Secondary

End point timeframe:

Any time from randomisation to the end of follow-up

End point values	Ongoing triple therapy	PI monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	296		
Units: Subjects				
Reached endpoint	7	12		
Did not reach endpoint	284	284		

Statistical analyses

Statistical analysis title	Analysis of Serious non-AIDS event
Comparison groups	Ongoing triple therapy v PI monotherapy

Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	Fisher exact

Secondary: CD4 change from baseline

End point title	CD4 change from baseline

End point description:

Patients without data at week 144 visit or a later time-point were excluded

End point type	Secondary

End point timeframe:

Groups were compared by use of mean change from baseline and linear regression; we estimated change from baseline to the last
available visit at which a measurement was done at or after week 144 (we did not include patients without such data).

End point values	Ongoing triple therapy	PI monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	283	287		
Units: cells per mm^3				
arithmetic mean (standard error)	93 (± 10)	109 (± 9)		

Statistical analyses

Statistical analysis title	Analysis of CD4 change from baseline
Comparison groups	Ongoing triple therapy v PI monotherapy
Number of subjects included in analysis	570
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	42

Secondary: Estimated glomerular filtration rate change

End point title	Estimated glomerular filtration rate change

End point description:

Groups were compared by use of mean change from baseline and linear regression.

End point type	Secondary

End point timeframe:

From randomisation to the last available visit at which a measurement was done at or after week 144.

End point values	Ongoing triple therapy	PI monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	283	286		
Units: mL/min per 1.73 m²				
arithmetic mean (standard error)	-5.1 (± 0.7)	-3.8 (± 0.7)		

Statistical analyses

Statistical analysis title	Analysis of eGFR change from baseline

Statistical analysis description:

Groups were compared by use of mean change from baseline and linear regression; we estimated change from baseline to the last available visit at which a measurement was done at or after week 144 (we did not include patients without such data).

Comparison groups	Ongoing triple therapy v PI monotherapy
Number of subjects included in analysis	569
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	3.15

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Any time from randomisation to the patient's last visit at or before 1. Nov 2013	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15

Reporting groups	
Reporting group title	Ongoing triple therapy
Reporting group description:	
Active control	
Reporting group title	PI monotherapy
Reporting group description:	
Experimental arm	

Serious adverse events	Ongoing triple therapy	PI monotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 291 (15.46%)	56 / 296 (18.92%)	
number of deaths (all causes)	1	6	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angiosarcoma metastatic			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Carcinoma in situ			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoma in situ of skin			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			

subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastatic neoplasm			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Small cell carcinoma			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Eye haemorrhage			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Appendicectomy			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal transplant			

subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gestational diabetes			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			

subjects affected / exposed	0 / 291 (0.00%)	2 / 296 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Depression suicidal			
subjects affected / exposed	0 / 291 (0.00%)	2 / 296 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric symptom			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			

Diverticulitis Meckel's			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand mal convulsion			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Headache			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normal pressure hydrocephalus			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Temporal arteritis			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 291 (0.34%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hodgkin's disease			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphogranuloma venereum			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Ear infection			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mastoid abscess			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Keratoconus			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 291 (0.34%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 291 (0.00%)	2 / 296 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal cancer stage IV			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Campylobacter gastroenteritis			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 291 (0.34%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Cellulitis			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 291 (0.00%)	2 / 296 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	2 / 291 (0.69%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ongoing triple therapy	PI monotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 291 (8.93%)	31 / 296 (10.47%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	
Meningioma			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences (all)	0	1	
Prostate cancer			
subjects affected / exposed	2 / 291 (0.69%)	1 / 296 (0.34%)	
occurrences (all)	2	1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 291 (0.69%)	0 / 296 (0.00%)	
occurrences (all)	2	0	
Hypertension			
subjects affected / exposed	3 / 291 (1.03%)	0 / 296 (0.00%)	
occurrences (all)	3	0	
Surgical and medical procedures			
Peripheral nerve decompression			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences (all)	0	1	
General disorders and administration			

site conditions			
Influenza like illness			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Crohn's disease			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences (all)	0	1	
Erythema nodosum			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	
Myasthenia gravis			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	
Depressed mood			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	1 / 291 (0.34%)	4 / 296 (1.35%)	
occurrences (all)	1	4	
Depression suicidal			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences (all)	0	2	
Stress			

subjects affected / exposed	1 / 291 (0.34%)	1 / 296 (0.34%)	
occurrences (all)	1	1	
Suicidal ideation			
subjects affected / exposed	1 / 291 (0.34%)	1 / 296 (0.34%)	
occurrences (all)	1	1	
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	2 / 291 (0.69%)	0 / 296 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Ligament rupture			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	
Wrist fracture			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 291 (0.00%)	2 / 296 (0.68%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Drug rash			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	
Jaundice			

subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Viral labyrinthitis			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	
Oesophageal perforation			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	
Hepatitis			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	
Hepatitis C			
subjects affected / exposed	0 / 291 (0.00%)	2 / 296 (0.68%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Basal cell carcinoma			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences (all)	0	1	
Skin oedema			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences (all)	0	1	

Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences (all)	0	1	
Urethral stenosis			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Cushing's syndrome			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences (all)	0	1	
Diabetes mellitus			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	1 / 291 (0.34%)	1 / 296 (0.34%)	
occurrences (all)	2	1	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	
Polyarthritis			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	
Sciatica			
subjects affected / exposed	0 / 291 (0.00%)	2 / 296 (0.68%)	
occurrences (all)	0	2	
Infections and infestations			
Herpes zoster			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences (all)	0	1	
Nasopharyngitis			

subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Cushing's syndrome			
subjects affected / exposed	0 / 291 (0.00%)	1 / 296 (0.34%)	
occurrences (all)	0	1	
Facial wasting			
subjects affected / exposed	1 / 291 (0.34%)	0 / 296 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 December 2008	Protocol version 2.0: The amendment to the trial protocol was proposed following the first meeting of the PIVOT IDMC and TSC in September 2008. At this meeting and after ongoing discussions with the site investigators, several changes were agreed with the aim to facilitate recruitment, clarify management strategy and maximise the generalisability and importance of the trial findings.
23 April 2010	Protocol version 3.0: Most changes were minor editorial and procedural changes that do not impact in any significant way on the conduct of the trial. Two major changes were made: Firstly, the sections of the protocol concerning the definition and management of viral load rebounds was re-written to clarify the language and to make the procedures more explicit. This arose as a result of a request from the Independent Data Monitoring Committee (meeting on 11 February 2010) to re-consider procedures and definitions around virological rebound in order to address the considerable diversity of practice at clinical sites that frequently did not follow the protocol. The changes will improve the quality of the data that will be gathered from the trial, and will not adversely impact patient safety. Secondly, we have revised the sample size of the trial. From the emerging literature on PI monotherapy and observations within the trial so far, we believe that the event rate (10% over 3 years) that we originally projected for the primary endpoint of the trial is too high. Based on several recently presented studies, we now believe the event rate is likely to be closer to 3%. We have therefore reviewed the sample size calculations for the trial, and the Trial Steering Committee recommended at its meeting on 2 March 2010 that the sample size be increased from 400 to 560 in order that the trial will be able to fulfil its primary objective of demonstrating non-inferiority of PI monotherapy to standard of care.
22 July 2013	Protocol version 4.0: Most changes were minor editorial and procedural changes that do not impact in any significant way on the conduct of the trial. However, in one area the protocol has changed substantially: The Trial Management Group proposed that the PIVOT trial be extended for up to a further 5 years. This would be in the form of an annual review of the clinical case sheets of PIVOT patients (both arms, and irrespective of treatment changes). Following the last trial visit, this proposed extension phase will continue for up to a further 5 years in which basic treatment and clinical outcome data will continue to be collected. Patients will not be required to attend any specific visits as part of this extension phase, the data will be collected via retrospective review of routine clinic notes. No reporting of serious adverse events will be required during this extension phase. The rational for the trial extension is that PIVOT is by far the largest and longest randomised controlled trial of PI monotherapy ever done, but even if the trial clearly shows that this treatment option is non-inferior to standard of care, questions may still remain about additional potential longer term advantages or disadvantages of PI monotherapy.

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/26423649

http://www.ncbi.nlm.nih.gov/pubmed/26966125

http://www.ncbi.nlm.nih.gov/pubmed/27456983

http://www.ncbi.nlm.nih.gov/pubmed/29428459