HEALTH TECHNOLOGY ASSESSMENT

VOLUME 20 ISSUE 21 MARCH 2016
ISSN 1366-5278

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National Institute for Health Research

DOI 10.3310/hta20210

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Declared competing interests of authors: none

Published March 2016
DOI: 10.3310/hta20210

This report should be referenced as follows:

Paton NI, Stöhr W, Oddershede L, Arenas-Pinto A, Walker S, Sculpher M, *et al*. The Protease Inhibitor Monotherapy Versus Ongoing Triple Therapy (PIVOT) trial: a randomised controlled trial of a protease inhibitor monotherapy strategy for long-term management of human immunodeficiency virus infection. *Health Technol Assess* 2016;**20**(21).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.027

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 06/403/90. The contractual start date was in July 2008. The draft report began editorial review in August 2014 and was accepted for publication in December 2014. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

The Protease Inhibitor Monotherapy Versus Ongoing Triple Therapy (PIVOT) trial: a randomised controlled trial of a protease inhibitor monotherapy strategy for long-term management of human immunodeficiency virus infection

Nicholas I Paton,[1,2]* Wolfgang Stöhr,[1] Lars Oddershede,[3] Alejandro Arenas-Pinto,[1] Simon Walker,[4] Mark Sculpher[4] and David T Dunn[1] on behalf of the PIVOT trial team†

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Background: Standard-of-care antiretroviral therapy (ART) for human immunodeficiency virus (HIV) infection uses a combination of drugs, until now considered essential to minimise treatment failure and development of drug resistance. Protease inhibitors (PIs) are potent with a high genetic barrier to resistance and have the potential for use as monotherapy after viral load (VL) suppression achieved on combination therapy. However, longer-term resistance and toxicity risks are uncertain.

Objective: To compare the effectiveness, toxicity profile and cost-effectiveness of PI monotherapy with those of standard-of-care triple therapy in a pragmatic long-term clinical trial.

Design: Open-label, parallel-group, randomised controlled trial.

Setting: Forty-three HIV clinical centres in the UK NHS.

Participants: HIV-positive adults taking standard combination ART with a suppressed VL for ≥ 6 months.

Interventions: Patients were randomised to maintain ongoing triple therapy (OT) or switch to a strategy of physician-selected ritonavir-boosted PI monotherapy (PI-mono), with prompt return to combination therapy in the event of VL rebound.

Main outcome measures: The primary outcome was reduction of future drug options, defined as new intermediate-/high-level resistance to one or more drugs to which the patient's virus was considered to be sensitive at trial entry (non-inferiority comparison, 10% margin). Secondary outcomes included confirmed virological rebound, serious drug- or disease-related complications, total grade 3 or 4 adverse events (AEs), neurocognitive function change, cluster of differentiation 4 (CD4) cell count change, change in health-related quality of life, cardiovascular risk change, health-care costs and health economic analysis.

Results: In total, 587 participants were randomised (77% male, 68% white) to OT ($n = 291$) or PI-mono ($n = 296$) and followed for a median of 44 months, of whom 2.7% withdrew/were lost to follow-up. One or more episodes of confirmed VL rebound were observed in eight patients (Kaplan–Meier estimate 3.2%) in the OT group and 95 patients (35.0%) in the PI-mono group [absolute risk difference 31.8%, 95% confidence interval (CI) 24.6% to 39.0%; $p < 0.001$]. PI-mono patients who changed to ART after VL rebound all resuppressed (median 3.5 weeks). The proportions with loss of a future drug option at 3 years were 0.7% in the OT group and 2.1% in the PI-mono group (difference 1.4%, (95% CI –0.4% to 3.4%); non-inferiority demonstrated). There were no significant differences in serious disease complications between groups or in the frequency of grade 3 or 4 clinical AEs (16.8% OT group vs. 22% PI-mono group; absolute risk difference 5.1%, 95% CI –1.3% to 11.5%; $p = 0.12$). Overall, the PI-mono strategy was shown to be cost-effective compared with OT under most scenarios explored. PI-mono was cost saving because of the large savings in ART drug costs while being no less effective in terms of quality-adjusted life-years in the within-trial analysis and only marginally less effective when extrapolated to lifetime outcomes.

Conclusions: PI monotherapy, with prompt reintroduction of combination therapy for VL rebound, was non-inferior to combination therapy in preserving future treatment options and is an acceptable and cost-effective alternative for long-term management of HIV infection.

Trial registration: Current Controlled Trials ISRCTN04857074.

Funding: This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 20, No. 21. See the NIHR Journals Library website for further project information.

Contents

List of tables

List of figures

List of abbreviations

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
BHIVA	British HIV Association
BNF	*British National Formulary*
cART	combination antiretroviral therapy
CD4	cluster of differentiation 4
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNS	central nervous system
CSF	cerebrospinal fluid
CVD	cardiovascular disease
DNA	deoxyribonucleic acid
DRV	darunavir
eGFR	estimated glomerular filtration rate
EQ-5D-3L	European Quality of Life-5 Dimensions 3 Level
GEE	generalised estimating equation
GLM	generalised linear model
GP	general practitioner
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IDMC	Independent Data Monitoring Committee
LPV	lopinavir
MI	multiple imputation
MOS-HIV	Medical Outcomes Study HIV Health Survey
NNRTI	non-nucleoside reverse transcriptase inhibitor
NPZ-5	neurocognitive performance *z*-score 5
NRTI	nucleoside reverse transcriptase inhibitor
OT	ongoing triple therapy
PBMC	peripheral blood mononuclear cell
PI	protease inhibitor
PI-mono	ritonavir-boosted protease inhibitor monotherapy
PIVOT	Protease Inhibitor Monotherapy Versus Ongoing Triple Therapy
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SAE	serious adverse event
SD	standard deviation
SE	standard error
TSC	Trial Steering Committee
UK-CAB	UK Community Advisory Board
VL	viral load

Plain English summary

Human immunodeficiency virus (HIV) treatment uses a combination of three medicines. If treatment is not powerful enough then the HIV virus rebounds and often becomes resistant to drugs and so the person has fewer drug options available for the future. Protease inhibitors (PIs) are very potent and it is very hard for the virus to develop resistance to them. Once the standard three-drug combination has suppressed the virus, the PI alone (as 'monotherapy') may be able to keep the virus suppressed and prevent resistance.

We tested this in a trial carried out in 43 clinics across the UK in which 587 HIV-positive people on standard treatment with suppressed virus were allocated by chance (half to each group) to either continue that standard treatment or switch to PI monotherapy. They were followed for up to 5 years to see which group ended up worse off in terms of the number of future drug options that they had lost through developing resistance. The trial found that people who were allocated to PI monotherapy lost very few future drug options – no more than did those on the standard treatment. There were also some small advantages (such as a slight reduction in long-term kidney damage).

In summary, the trial has shown that PI monotherapy with regular checking of the HIV virus level and switch back to combination treatment if needed is an acceptable option for the long-term management of HIV infection and is also cost-effective.

Scientific summary

Background

Standard-of-care antiretroviral therapy (ART) for human immunodeficiency virus (HIV) infection uses a combination of drugs, an approach until now considered essential to minimise treatment failure and development of drug resistance. The 2013 British HIV Association (BHIVA) treatment guidelines recommend that an initial treatment regimen should contain two nucleoside reverse transcriptase inhibitors (NRTIs) together with a non-NRTI (NNRTI) drug (efavirenz), a ritonavir-boosted protease inhibitor (PI) [atazanavir or darunavir (DRV)] or an integrase strand-transfer inhibitor (raltegravir). In practice, the most commonly used third drug (on the backbone of two NRTIs) prescribed in the UK has been efavirenz.

Protease inhibitors have very high antiviral activity, have the highest genetic barrier to resistance of all HIV drugs and are the only drugs that act at multiple steps of the HIV lifecycle, thus giving them the potential to be used alone as monotherapy. A randomised controlled trial that examined the use of PI monotherapy in treatment-naive patients showed clearly inferior performance with the generation of substantial drug resistance. However, several other trials in which patients switched to PI monotherapy after achieving full viral load (VL) suppression have produced more encouraging results, in some cases demonstrating non-inferiority compared with standard-of-care (for a primary outcome of short-term VL suppression). However, these trials have used a single protocol-specified PI, lopinavir/ritonavir or DRV/ritonavir, usually mandated for both the monotherapy and the standard-of-care group (thus not resembling standard practice in the UK). Furthermore, the trials have been based on a primary end point of short-term VL suppression (usually at 48 weeks), whereas it is the preservation of adequate future treatment options and the minimisation of toxicity that really matter in long-term HIV care. Although data supporting longer-term meaningful outcomes are limited, PI monotherapy is being increasingly used in clinical practice in the UK and in some European countries.

Objective

To compare the effectiveness, toxicity profile and cost-effectiveness of PI monotherapy with those of standard-of-care triple therapy in a pragmatic long-term clinical trial based in routine clinical care.

Design

Open-label, parallel-group, randomised controlled trial.

Setting

Forty-three HIV clinical centres in the UK NHS with wide geographical representation and including diverse patient populations (14 centres in London, 29 outside London).

Participants

The trial enrolled HIV-positive adults aged > 18 years who had been on ART consisting of two NRTIs and one NNRTI or a PI for at least 24 weeks with no change in the previous 12 weeks and who had a VL of < 50 copies/ml at, and for at least 24 weeks before, screening. The main exclusion criteria were known major PI resistance mutation(s) on previous resistance testing; previous ART change for unsatisfactory virological response; concomitant medication with PI interactions; and central nervous system disease, cardiovascular disease or diabetes.

Interventions

Participants were randomised to maintain ongoing triple therapy (OT) or switch to a strategy of physician-selected ritonavir-boosted PI monotherapy (PI-mono) with prompt return to combination therapy (reintroduction of NRTIs, switch of PI to NNRTI discretionary) in the event of VL rebound (defined as three consecutive tests at > 50 copies/ml, including one repeat on the first sample if available). VL was monitored every 12 weeks.

Protease inhibitor substitution was allowed for toxicity or convenience.

Main outcome measures

The primary outcome was loss of future drug options, defined as new intermediate-/high-level resistance to one or more drugs to which the patient's virus was considered to be sensitive at trial entry (non-inferiority comparison, 10% margin). The primary analysis included all resistance mutations detected, whereas a predefined sensitivity analysis excluded resistance mutations that were detected to classes of drugs that the patient was not receiving during the trial (and which likely were archived mutations). Secondary outcomes included confirmed VL rebound, serious drug- or disease-related complications, total grade 3 or 4 adverse events (AEs), neurocognitive function change (using a standardised test battery assessing five neurocognitive domains), cluster of differentiation 4 (CD4) cell count change, change in health-related quality of life, cardiovascular risk change, health-care costs and health economic analysis.

Results

In total, 587 participants were randomised (77% male, 68% white) to OT ($n = 291$) or PI-mono ($n = 296$) and followed for a median of 44 months, of whom 2.7% withdrew/were lost to follow-up. One or more episodes of confirmed VL rebound were observed in eight patients (Kaplan–Meier estimate 3.2%) in the OT group and 95 patients (35.0%) in the PI-mono group [absolute risk difference 31.8%, 95% confidence interval (CI) 24.6% to 39.0%; $p < 0.001$]. PI-mono patients who changed to combination ART after VL rebound all resuppressed (median 3.5 weeks). The proportions of participants with loss of a future drug option at 3 years were 0.7% in the OT group and 2.1% in the PI-mono group [difference 1.4% (95% CI –0.4% to 3.4%); non-inferiority demonstrated]. In the prespecified sensitivity analysis, in which mutations that were likely archived were excluded, the proportions of patients with loss of a future drug option at the end of trial follow-up were 1.5% in the OT group and 1.0% in the PI-mono group [difference –0.4% (95% CI –2.1% to 1.4%); non-inferiority also demonstrated]. Only one participant in the PI-mono group developed resistance to the PI that they were taking: a participant taking atazanavir monotherapy who developed the I50L mutation, predicted to confer high-level resistance to atazanavir.

There were no significant differences in serious drug- or disease-related complications between the groups. Although there were more deaths in the PI-mono group (six vs. one), these were of diverse aetiology, often with clear non-HIV-related risk factors present, and the numerical difference was not statistically significant. The numbers of serious adverse events and clinical grade 3 and 4 AEs did not differ between the groups, but there were fewer total grade 3 or 4 AEs in the PI-mono group, the difference reflecting fewer laboratory events. Fewer patients in the PI-mono group experienced an estimated glomerular filtration rate below 60 ml/minute/1.73 m^2 during follow-up (10% OT group vs. 5% PI-mono group; difference –4.6%, 95% CI –8.8% to –0.4%; $p = 0.033$). There were no differences between the groups in the proportions of patients with symptomatic peripheral neuropathy, facial lipoatrophy or abdominal fat accumulation or in the summary scores for neurocognitive function, cardiovascular disease risk or quality of life or in the mean CD4 cell count change.

Overall, the PI-mono strategy was shown to be cost-effective compared with OT under most scenarios explored. The PI-mono strategy was cost saving because of large savings in ART drug costs while being no less effective in terms of quality-adjusted life-years in the within-trial analysis and only marginally less effective with modelling.

Conclusions

Protease inhibitor monotherapy, with regular VL monitoring and prompt reintroduction of combination therapy for VL rebound, was non-inferior to combination therapy in preserving future treatment options and is an acceptable and cost-effective alternative for long-term management of HIV infection.

Trial registration

This trial is registered as ISRCTN04857074.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Human immunodeficiency virus epidemiology and care in the UK

At the end of 2012 there were an estimated 100,000 people living with human immunodeficiency virus (HIV) in the UK, of whom approximately 80% have been diagnosed and seen for HIV-related care. The annual number of new HIV diagnoses made in the UK continues to rise, with 6360 new cases in 2012,[1] and as more people receive effective treatment the number of deaths continues to fall. Thus, the number of people receiving treatment and the already substantial burden on the NHS will continue for the foreseeable future. The cost of providing care and treatment to people living with HIV in the UK increased by about 600% from 1997 to 2010, when £762M was spent, mainly on antiretroviral therapy.[2]

Principles of antiretroviral therapy

A range of drugs are available that are active in blocking the replication of HIV. Current HIV treatment guidelines recommend a combination of two drug classes for the initiation and maintenance of antiretroviral therapy (ART).[3,4] The principle of combining drugs with different mechanisms of action to increase potency and reduce the selection of drug-resistant mutants is common to the treatment of many infectious diseases. However, the need for combination therapy for HIV may be reduced after the initial period of treatment, once viral load (VL) has been suppressed and the risk of de novo resistance generation diminishes.

Recommendations for the threshold at which HIV treatment should be started differ internationally, with the current US treatment guidelines[4] recommending starting all HIV-infected individuals on treatment, regardless of their cluster of differentiation 4 (CD4) cell count, to reduce the risk of disease progression, and the UK guidelines[3] recommending starting at a CD4 cell count of 350 cells/mm^3. This is based predominantly on data from large cohorts which show that starting ART at CD4 cell counts of > 500 cells/mm^3 was associated with slower HIV disease progression measured by acquired immunodeficiency syndrome (AIDS) events, HIV-associated mortality or all-cause mortality.[5,6] However, substantive evidence is now available from a large randomised controlled trial (RCT), the Strategic Timing of AntiRetroviral Treatment (START) trial, that demonstrates that initiating ART at CD4 cell counts of > 500 cells/mm^3 is of benefit.[7] Aside from potential benefits to the individual, early initiation of ART has been shown to effectively reduce HIV sexual transmission and may diminish population-level incidence of HIV infection.[8] Once started, treatment needs to be continued indefinitely – the Strategies for Management of Antiretroviral Therapy (SMART) trial showed inferior outcomes with treatment interruption, even at high CD4 cell counts.[9]

As a result of the move towards extending therapy exposure (start earlier and continue indefinitely) is the realisation that patients are now facing the prospect of taking ART for decades. Maximising long-term durability, preserving a viable sequence of future drug options and minimising long-term side effects are becoming increasingly important considerations.

New strategic approaches

Much of the current pharmaceutical company-driven research as well as investigator-initiated research is now designed to look at switching drugs or compare regimens for toxicity or tolerability advantages. The search for cost-effective approaches to care, including ways of containing drug costs and approaches to simplify monitoring and follow-up, is also an important focus of current research.

The availability of effective and well-tolerated newer drug options that act on different targets, such as integrase inhibitors, has not only increased the treatment options available but also led to re-examination of the paradigm of care [treatment with triple therapy, consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) and a non-NRTI (NNRTI) or protease inhibitor (PI)] that has changed little in the last decade. The availability of more treatment options may have also allowed some flexibility to accept a small risk of treatment failure in a regimen that has fewer side effects or that effectively preserves long-term treatment options in the vast majority.

Thus, research into more innovative uses of current drugs, as well as ways of combining or sequencing drugs to maximise long-term outcomes (preserving viable treatment options, minimising toxicity, minimising cost), is increasingly important. Given that treatment interruption is not a sensible option, treatment simplification studies form an increasingly important aspect of the HIV treatment research agenda, not only for individual patients but also for health-care policy.[2,10,11] The most promising candidates for treatment simplification are undoubtedly the PIs.

Previous trials of protease inhibitor monotherapy

Protease inhibitors have very high antiviral activity, have the highest genetic barrier to resistance of all HIV drugs and are the only drugs that act at multiple steps of the HIV lifecycle, thus giving them the potential to be used alone as monotherapy.[12] A RCT that examined the use of PI monotherapy for treatment-naive patients showed clearly inferior performance, with the generation of substantial resistance.[13] However, other trials in which patients switch to PI monotherapy after achieving full VL suppression have been more successful. These trials have generally used lopinavir (LPV)/ritonavir and darunavir (DRV)/ritonavir monotherapy and have evaluated non-inferiority based on VL suppression in plasma at weeks 48 or 96 after switching from combination antiretroviral therapy (cART). Results have been generally favourable, although several studies have failed to demonstrate non-inferiority compared with standard-of-care. *Table 1* summarises the published RCTs on ritonavir-boosted PI monotherapy as a simplification strategy.

Small single-arm studies ($n = 30$–36) have explored ritonavir-boosted atazanavir simplification in patients effectively suppressed on cART, showing effective preservation of virological suppression in 64–80% of patients with no evidence of selection of PI-resistance mutations in those who developed VL rebound.[28–30]

A systematic review and meta-analysis of RCTs identified 10 trials involving 1189 patients comparing three different PIs used as monotherapy against a standard regimen of a PI plus two NRTIs.[31] With the most conservative approach (VL < 50 copies/ml on two consecutive measurements), the risk ratios for effective viral suppression at 48 weeks for PI monotherapy compared with cART were 0.94 [95% confidence interval (CI) 0.89 to 1.00] in the intention-to-treat analysis and 0.93 (95% CI 0.90 to 0.97) in the per-protocol analysis. Reintroduction of cART in 44 patients with virological failure led to de novo viral suppression in 93%.

Given the contradictory findings and the small size of the trials, PI monotherapy has not been widely adopted in HIV treatment guidelines. Only the European guidelines[32] consider PI monotherapy an option and then only for selective patient groups.

TABLE 1 Summary of RCTs of PI monotherapy as a switch strategy in patients with virological suppression

Study	*n* (monotherapy vs. other)	Drug vs. comparator	Eligibility	End point	Results
Arribas 2005,[14] Pulido 2008,[15,16] (OK study)	21 vs. 21	LPV/r vs. LPV/r plus two NRTIs	Experienced without PI failure VL < 50 copies/ml for > 6 months LPV/r plus two NRTIs for > 1 month	VL < 500 copies/ml at week 48 (ITT, M or change = F) Failure = VL > 500 copies/ml × 2 that could not resuppress (< 50 copies/ml) with NRTIs	No difference in virological suppression between arms at week 48 (81% and 95% in patients on LPV/r monotherapy and LPV/r plus two NRTIs respectively; $p = 0.34$) No major PI mutations were found even after 4 years' follow-up
Pulido 2008,[15] Arribas 2009[17] (OK04 study)	103 vs. 102	LPV/r vs. LPV/r plus two NRTIs	Experienced without PI failure VL < 50 copies/ml for > 6 months LPV/r plus two NRTIs for > 1 month	VL < 500 copies/ml at week 48 (ITT, M or change = F) Failure = VL > 500 copies/ml × 2 that could not resuppress (< 50 copies/ml) with NRTIs	No difference in virological suppression between arms by week 48 (94% and 90% in patients on LPV/r monotherapy and LPV/r plus two NRTIs respectively) with upper limit of 95% CI for difference of 3.4% Using < 50 copies/ml, 85% and 90% of patients on LPV/r monotherapy and LPV/r plus two NRTIs, respectively, had an undetectable VL at week 48 ($p = 0.31$; upper limit of 95% CI for difference of 14%) By week 96, 87% on monotherapy ($n = 100$) and 78% on triple therapy ($n = 98$; 95% CI –20% to +1.2%) showed effective virological suppression Using < 50 copies/ml, 77% and 78% of patients on LPV/r monotherapy and LPV/r plus two NRTIs, respectively, had an undetectable VL at week 96

continued

TABLE 1 Summary of RCTs of PI monotherapy as a switch strategy in patients with virological suppression (*continued*)

Study	*n* (monotherapy vs. other)	Drug vs. comparator	Eligibility	End point	Results
Nunes 2009[18] (KalMo study)	30 vs. 30	LPV/r vs. continued HAART	No history of VF VL < 80 copies/ml for > 6 months CD4 cell count of > 200 cells/mm^3	VL < 80 copies/ml at week 96 (ITT, M = F)	No difference in virological suppression between arms by week 96 (80.0% and 86.6% in patients on LPV/r monotherapy and LPV/r plus two NRTIs respectively; $p = 0.48$) There was one virological failure (defined as a VL < 500 copies/ml) in each arm. No major PI mutations were found
Meynard 2010[19] (KALESOLO study)	87 vs. 99	LPV/r vs. continued HAART	Experienced VL < 50 copies/ml for ≥ 6 month	VL < 50 copies/ml at week 48	LPV/r monotherapy did not achieve non-inferiority vs. cART for maintaining plasma VL at < 50 copies/ml No major PI mutations were found
Gutmann 2010[20] (MOST study)	29 vs. 31	LPV/r vs. continued HAART	Experienced CD4 cell count of ≥ 100 cells/mm^3 VL < 50 copies/ml for ≥ 6 months	Treatment failure in the CNS or genital compartment (2 × VL > 400 copies/ml)	Trial ended prematurely when six patients on monotherapy demonstrated VF in plasma
Cahn 2011[21]	41 vs. 39	LPV/r vs. LPV/r plus two NRTIs	Experienced No history of VF HAART for ≥ 6 months VL < 50 copies/ml for ≥ 3 months	VL < 200 copies/ml at day 360	No difference in virological suppression between arms by day 360 (80% and 86.6% in patients on LPV/r monotherapy and LPV/r plus two NRTIs respectively; $p = 0.611$) Using < 50 copies/ml, 92% and 95% of patients on LPV/r monotherapy and LPV/r plus two NRTIs, respectively, had an undetectable VL at day 360 ($p = 0.671$)

Study	*n* (monotherapy vs. other)	Drug vs. comparator	Eligibility	End point	Results
Arribas 2010,[22] Clumeck 2011,[23] Arribas 2012[24] (MONET study)	127 vs. 129	DRV/r vs. DRV/r plus two NRTIs	Experienced HAART plus two NRTIs plus either NNRTI or PI at screening No previous use of DRV VL < 50 copies/ml for ≥ 6 months No previous VF	Proportion with VL < 400 copies/ml at week 48 Treatment failure: 2 × VL > 50 copies/ml; discontinuation of randomised therapy (time to loss of virological response); stopping DRV/r or starting NRTIs in the monotherapy arm; or stopping NRTIs in the control arm (switches in NRTIs permitted)	Non-inferiority demonstrated at week 48 in the per-protocol and ITT and by switch = failure analyses (86.2% vs. 87.8%, 84.3% vs. 85.3% and 93.5 vs. 95.1% in the monotherapy and triple therapy arms respectively) Non-inferiority not demonstrated at week 96 in ITT analysis 7/8 with detectable viraemia resuppressed with NRTI intensification 47 genotyped (20 in monotherapy arm): only one patient per arm had any evidence of genotypic resistance; both patients regained suppression without change in therapy By week 144, 69% and 75% of patients on monotherapy and triple therapy, respectively, had a VL of < 50 copies/ml (ITT switch = failure); these values were 84% and 83.5% if switches were not considered failures

continued

TABLE 1 Summary of RCTs of PI monotherapy as a switch strategy in patients with virological suppression (*continued*)

Study	*n* (monotherapy vs. other)	Drug vs. comparator	Eligibility	End point	Results
Katlama 2010,[25] Valantin 2012[26] (MONOI study)	112 vs. 133	DRV/r vs. DRV/r plus two NRTIs	Experienced DRV naive VL < 50 copies/ml at screening VL < 400 copies/ml for ≥ 18 months No PI failure CD4 cell count nadir of > 50 cells/mm^3 All patients suppressed on DRV/r prior to randomisation	Proportion with VL of < 400 copies/ml at week 48 Treatment failure: 2 × VL > 400 copies/ml; treatment modification; withdrawal	Non-inferiority demonstrated at week 48 in the per-protocol analysis (94% and 99% of patients on DRV/r monotherapy and triple therapy, respectively, had undetectable VL; 90% CI for the difference –9.1 to 0.8%) Non-inferiority not demonstrated at week 48 in ITT analysis No resistance to PI emerged by week 48 No difference in virological suppression between arms by week 96 (88% and 84% in patients on DRV/r monotherapy and triple therapy respectively; $p = 0.42$)
Echeverria 2010[27]	17 vs. 11	SQV/r vs. continued HAART	Experienced VL < 50 copies/ml for ≥ 3 months No history of VF	VF at week 48	Only one patient from the SQV/r group experienced virological failure at week 48. A similar mean increase in CD4 cell count was observed in both groups at week 48

CNS, central nervous system; DRV/r, darunavir/ritonavir; HAART, highly active antiretroviral therapy; ITT, intention to treat; ITT, M = F, intention-to-treat analysis, for which missing values are treated as failure; LPV/r, lopinavir/ritonavir; M or change = F, missing values or treatment change regarded as failure; MOST, Monotherapy Switzerland/Thailand; VF, virological failure.

Virological and resistance concerns over protease inhibitor monotherapy

A proportion of patients may not be able to maintain full viral suppression on PI monotherapy and, if not addressed, there is the theoretical risk that ongoing viral replication may lead to the selection of resistance mutations. However, the trials summarised in *Table 1* as well as observational studies have shown that the selection of major PI mutations in patients with detectable viraemia while on PI monotherapy occurs only rarely.[33,34] In addition, complete concordance between circulating and cell-associated virus genotypes has been reported in patients on DRV monotherapy, with no major DRV-selected resistance mutations in peripheral blood mononuclear cells (PBMCs), offering additional reassurance that exposure to PI monotherapy, at least with DRV, may not compromise future antiretroviral treatment options.[35]

Although resistance is rare, several studies have shown that some mutations at the *gag* cleavage site might reduce sensitivity to PI-based regimens. In the MONOI trial ($n = 255$),[36] nine participants developed virological failure (defined as VL > 400 copies/ml in two consecutive samples) but major DRV-selected mutations could not be demonstrated in any of them using standard sequencing. However, by doing protease gene clonal analysis, the authors found that the virus of one of the nine patients with virological failure presented minority variants, with DRV resistance mutations at positions 32, 47 and 50 but no mutations in the *gag* region.

Although trials have usually shown very similar rates of VL suppression with PI monotherapy, there is a theoretical concern that there may be ongoing low-level HIV replication that could cause disease pathology. In both the MONET[37] and MONOI[38] trials no difference in the change from baseline of level of proviral deoxyribonucleic acid (DNA) (cellular integrated HIV-1 DNA) in PBMCs was observed between patients on DRV monotherapy and those on triple therapy. Furthermore, in an observational study,[39] no difference in tonsil viral replication was observed between patients on NNRTI-based cART and patients on either DRV/r or LPV/r, but proviral DNA levels were found more frequently in patients on cART. Thus, there is no evidence for occult viral replication when patients have an undetectable VL on PI monotherapy.

Other concerns with protease inhibitor monotherapy

As a consequence of effective viral suppression, dementia and serious neurocognitive impairment that were frequently seen in patients with advanced HIV disease not receiving effective ART have become relatively rare in recent years.[40,41] Despite this, high rates of more subtle cognitive dysfunction in HIV-infected subjects are being increasingly described, with neurocognitive impairment rates approaching 50% in some cohorts. Several factors have been implicated in the evolution of neurocognitive impairment in the highly active antiretroviral therapy (HAART) era, including older age, a low nadir CD4 cell count, chronic hepatitis C virus (HCV) co-infection and possibly the use of antiretroviral regimens with poor central nervous system (CNS) penetration.[42] The penetration of PIs into the CNS is variable and generally inferior to that of the other main drug classes, thus raising the concern about the possibility of neurocognitive deterioration on PI monotherapy. Prior to this trial, this has not been systematically investigated with formal neurocognitive testing.

Data from RCTs have not shown consistent evidence for any excess risk of CNS adverse events (AEs) in patients on DRV and LPV monotherapy, although detectable HIV RNA in cerebrospinal fluid (CSF) of symptomatic patients has been reported.[43] The Monotherapy Switzerland/Thailand (MOST) trial[20] was stopped prematurely when six patients on LPV/ritonivir monotherapy developed virological failure in peripheral blood. CSF samples were available for five of these patients and detectable VL was also confirmed in these. However, the results of the MOST trial are not in agreement with data generated in previous studies and, as the study was interrupted, its findings are difficult to interpret.[44] Furthermore, cross-sectional data showed that, compared with patients on cART, effectively suppressed patients on PI monotherapy did not show any higher rate of neurocognitive impairment.[45]

Possible benefits of protease inhibitor monotherapy

Ritonavir-boosted PI monotherapy may reduce the risk of long-term toxicity associated with NRTIs and, in some cases, NNRTIs. In addition, PI monotherapy may possibly reduce the risk of long-term failure because of the high genetic barrier to resistance (compared with NRTIs and NNRTIs) and a better profile of preserved drug options for the future. Previous RCTs have not shown major differences in safety parameters between PI monotherapy and cART.

A further advantage is likely to be the reduction in treatment costs, although this may be offset by more frequent VL rebounds in patients on PI monotherapy leading to additional costs to health services. PI monotherapy as a strategy may be potentially cost saving if it can be implemented in a large group of patients on ART.[2]

Rationale for this trial

The previous randomised trials of PI monotherapy summarised earlier have shown high rates of short-term VL suppression, sometimes meeting non-inferiority criteria, but have not been of sufficient size and duration to address definitively the effects on long-term drug resistance, clinical disease progression and drug toxicity in clinical practice.[17,24,25,31,46] This trial was designed to be different in a number of respects from the previously completed or ongoing pharma-sponsored studies:

1. Whereas other studies have examined the effect of PI monotherapy per se, this trial was designed to examine the effectiveness of a *strategy* that includes prompt switch back to standard-of-care when PI monotherapy does not maintain full virological suppression of < 50 copies/ml.
2. Whereas previous or ongoing studies were/are focused on specific PI drugs and specified comparator regimens, this trial allows drug selection according to patient/physician preference and selection or switching of PIs for maximising tolerability; it is therefore more relevant to clinical practice.
3. Whereas other studies were of relatively short duration (1–2 years), this trial set out to have a relatively long-term follow-up perod (up to 5 years), which is important for assessing long-term consequences of this strategy.
4. Whereas other studies have focused on short-term VL end points (reflecting their commercial origin and single drug focus), this trial has an end point of clinical drug resistance, chosen to be most relevant to the long-term goal of maintaining effective treatment regimens.

The Protease Inhibitor Monotherapy Versus Ongoing Triple Therapy (PIVOT) trial was designed as a pragmatic RCT to evaluate relevant long-term outcomes in patients following a PI monotherapy strategy in routine clinical care centres across the UK.

The main trial objectives were to:

1. determine whether or not a strategy of switching to PI monotherapy is non-inferior to continuing triple drug therapy (the standard-of-care) in terms of the proportion of patients who maintain all of their available drug treatment options after at least 3 years of follow-up
2. compare the safety and toxicity of PI monotherapy with those of standard-of-care triple therapy over 3–5 years
3. assess the cost-effectiveness of PI monotherapy after 3 years' follow-up and to extrapolate to lifetime follow-up.

Chapter 2 Methods

This open-label randomised parallel-group trial (registered as ISRCTN04857074) was performed in 43 centres in the UK (sites listed in *Acknowledgements*).

Trial entry criteria

The trial enrolled HIV-positive adults aged > 18 years who had been on ART comprising two NRTIs and one NNRTI or one PI for at least 24 weeks with no change in the previous 12 weeks, who had a VL of < 50 copies/ml at and for at least 24 weeks before screening (one 'blip' to < 200 copies/ml allowed during this period if followed by two or more tests with a result of < 50 copies/ml), who had a CD4 cell count of > 100 cells/mm^3 at screening and who were willing to continue with their current ART or change according to the randomised allocation. Exclusion criteria were known major PI resistance mutation(s) on previous resistance testing (if performed; not mandated), previous ART change for unsatisfactory virological response (change for toxicity prevention/management or convenience permitted), PI allergy, concomitant medication with PI interactions, current or anticipated requirement for radiotherapy or cytotoxic chemotherapy, treatment for acute opportunistic infection within the previous 3 months, current or planned pregnancy, active substance abuse or psychiatric illness (that would, in the opinion of the investigator, prevent compliance with the protocol or assessments), history of HIV encephalopathy with a current deficit of > 1 in any domain of the Neuropsychiatric AIDS Rating Scale (NARS),[47,48] history of cardiovascular disease (CVD), 10-year absolute coronary heart disease risk of > 30% or risk of > 20% with diabetes or a family history of premature ischaemic heart disease/stroke,[49] insulin-dependent diabetes mellitus, active/planned HCV treatment, hepatitis B virus (HBV) surface antigen positive at screening or since HIV diagnosis (unless HBV DNA < 1000 copies/ml while off HBV-active drugs) or a fasting plasma glucose > 7.0 mmol/l at screening.

We chose to exclude patients with active substance use or psychiatric illness that was thought likely to prevent compliance with the protocol because we thought that it was paramount to conduct a definitive trial that answered the question of the risks for long-term treatment options arising from VL rebound and this would require very high levels of trial retention. We excluded patients with a high risk of CVD because of the concern that PIs may add to that risk, and it seemed inappropriate to randomise patients with CVD who were stable on relatively low-risk NNRTI-based regimens to a new regimen that might increase that risk. Most of the other inclusion and exclusion criteria are standard.

The protocol was approved by the Cambridgeshire 4 Research Ethics Committee and the Medicines and Healthcare products Regulatory Agency (MHRA) and all participants provided written informed consent.

Randomisation and treatment strategies

Participants were randomly assigned in a 1 : 1 ratio to maintain ongoing triple therapy (OT) or switch to ritonavir-boosted PI monotherapy (PI-mono). In the OT group, patients were managed using triple combination therapy regimens with changes allowed for toxicity, convenience or protocol-defined confirmed VL rebound (see *Assessments*). In the PI-mono arm, patients were switched to a single ritonavir-boosted PI (physician choice but ritonavir-boosted DRV 800 mg/100 mg once daily or ritonavir-boosted LPV 400 mg/100 mg twice daily were recommended). Patients switching from a NNRTI-based regimen continued on NRTIs for the first 2 weeks. PI substitution was allowed for toxicity or convenience. The strategy required prompt reintroduction of NRTIs (switch of PI to NNRTI discretionary) in the event of protocol-defined confirmed VL rebound (see *Assessments*), and patients were subsequently managed on combination therapy for the remainder of the trial. Subsequent switches for toxicity, convenience or VL failure were allowed, as for the OT group. The hypothesis was that PI-mono would be non-inferior to OT.

Randomisation was stratified by centre (nine groups) and baseline ART regimen (PI vs. NNRTI). The computer-generated, sequentially numbered randomisation list (permuted blocks of varying size) was preprepared by the trial statistician. Screening forms were faxed to a central trials unit, eligibility was confirmed and, on receipt of a baseline visit form, randomisation was performed by the trial manager who could access the next number but not the whole list.

Assessments

Study visits at baseline, weeks 4 and 8 (PI-mono only), week 12 and at every 12 weeks thereafter included assessment of clinical status, medication adherence (standardised questions), VL and CD4 cell count as well as safety blood tests (measured at the site laboratory). Visits at baseline, week 12, week 48 and every 48 weeks thereafter included additional assessments of 10-year CVD risk,[49] neurocognitive function (described below), symptomatic peripheral neuropathy (Brief Peripheral Neuropathy Screen)[50,51] and quality of life [self-completed Medical Outcomes Study HIV Health Survey (MOS-HIV)].[52]

Neurocognitive testing was performed by designated research staff at each study site after receiving appropriate training by the co-ordinating centre. The training procedures included a face-to-face session, a training video and practice of the tests with at least five work colleagues before being allowed to assess study participants, followed by yearly revision. Five cognitive domains were explored with three different tests: verbal learning and memory were assessed using Hopkins Verbal Learning Test – Revised (HVLT-R),[53] fine motor skills were assessed using the Grooved Pegboard Test[54] and attention and executive function were assessed using Colour Trails Tests 1 and 2 respectively.[55] Test performance was considered invalid if participants decided to abandon the test before completion, if investigators failed to comply with standard procedures according to the instructions, or if the test was interrupted because of external factors. In addition, all scores were centrally monitored and extreme results were investigated and excluded if considered to be related to any of the situations listed above. Only participants with complete cognitive testing results available were included in the analyses. Raw scores for each cognitive test were transformed to *z*-scores using the manufacturers' normative data[53–55] adjusted for age (all tests) and years of education (Colour Trails Tests) by subtracting the mean and dividing by the standard deviation (SD) of test scores in reference populations. For the Grooved Pegboard Test the *z*-score was obtained by taking the average of the *z*-scores for the dominant and non-dominant hands. A summary score was then calculated for each patient by averaging the *z*-scores of the five tests [neurocognitive performance *z*-score 5 (NPZ-5)].

Clinical and laboratory events were classified by each site according to standard diagnostic criteria in the protocol [based on Centers for Disease Control and Prevention (CDC) criteria for AIDS;[56] INSIGHT criteria for serious non-AIDS events;[57] and Division of AIDS (DAIDS) criteria for AEs][58] and were reviewed by an independent physician at the trial co-ordinating centre. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[59]

If VL was detectable at ≥ 50 copies/ml at any visit, the test was repeated (on the same sample if available or on a fresh sample draw if not). If the VL was < 50 copies/ml, routine follow-up resumed; if the VL was ≥ 50 copies/ml, adherence counselling was performed and the patient returned for a confirmatory VL test at least 4 weeks from the date of the first sample. If the VL was < 50 copies/ml on the confirmatory test, routine follow-up resumed; if the VL was ≥ 50 copies/ml (i.e. third consecutive test) this met the protocol definition of confirmed VL rebound and the patient was required to change therapy and a repeat VL test was performed 4 weeks later.

Genotypic resistance testing was performed on all confirmed VL rebound samples and on rebound samples that did not meet this definition but preceded treatment switch. Genotypic testing was carried out at site laboratories and was repeated at the central laboratory if local sequencing was unsuccessful. Drug susceptibility prediction used the Stanford algorithm.[60] When resistance mutations were identified, comparison was made with any pre-trial genotypic testing reports.

The primary outcome was loss of future drug options, defined as new intermediate-/high-level resistance to one or more drugs in contemporary use to which the patient's virus was considered to be sensitive at trial entry. Contemporary use was determined by current UK treatment guidelines,[3] with saquinavir added as this was taken by some participants during the trial. Interim data were reviewed approximately annually by an Independent Data Monitoring Committee (IDMC).

Secondary outcomes were the occurrence of serious drug or disease-related complications (death, serious AIDS-defining illness, serious non-AIDS-defining illness); the total number of grade 3 and 4 AEs; confirmed virological rebound (defined as above); CD4 cell count change from baseline; neurocognitive function change from baseline; cardiovascular risk change from baseline; and health-related quality of life (HRQoL) change from baseline (mental and physical health summary scores on the MOS-HIV questionnaire).

Additional specified safety outcomes included assessment of facial lipoatrophy, abdominal fat accumulation, peripheral neuropathy and eGFR.

Health-care costs were evaluated and a full health economic analysis performed as described in *Chapter 4*.

Sample size determination and statistical analysis

Assuming that 97% of patients in the OT group would maintain all future drug options (i.e. remain free of new resistance mutations) over 3 years,[16,22,25] we estimated that approximately 280 patients per group would be required to demonstrate non-inferiority of PI-mono, defined by the upper limit of the 95% CI (two-sided) for the difference in the proportion of patients who maintain all future drug options over 3 years (OT – PI-mono) being < 10% with 85% power and allowing 10% loss to follow-up. The 10% non-inferiority margin was chosen based on US Food and Drug Administration (FDA) guidance.[61,62]

All comparisons were as randomised (intention to treat). Statistical tests presented are two-sided and test the null hypothesis of no difference between randomised groups. The absolute difference between the groups in the reduction of future drug options was estimated using Kaplan–Meier analysis, with the 95% CI (two-sided) derived using bootstrap methods. The primary analysis included all new resistance mutations seen that conferred intermediate-/high-level drug resistance, but a sensitivity analysis was predefined in which loss of drug options was restricted to classes to which the patient was exposed during the trial (i.e. excluded mutations that were likely archived).

For secondary end points, binary outcome variables were compared between groups using the chi-squared test or Fisher's exact test and using logistic regression models for adjusted analyses; for continuous variables groups were compared using mean change from baseline and the *t*-test/linear regression [change was from baseline to the last available visit at which a measurement was performed or after week 144 (patients without such data were not included)]. Time-to-event outcomes were tested using a log-rank test. Poisson regression was used to compare incidence rates. Global tests of difference between randomised groups taking into account data at all follow-up time points were performed using generalised estimating equations (GEEs) (independent correlation structure, binomial or normal distribution as appropriate).

Patient and public involvement in the research

Given that this was a large UK-based trial looking at the long-term treatment of people living with HIV infection, it was considered critical from the outset to have involvement from the HIV community. An important consideration was that, in view of the cost-saving potential of the monotherapy approach, it was possible that the trial could at some stage be misrepresented as a cost-saving initiative and this perception might damage the trial. It was felt that engagement of the community was essential for maintaining the focus on the potential patient benefits, such as toxicity reduction, and ensuring that this message came across to the people in the trial as well as more broadly. The measures to engage the community are outlined briefly below.

The chief investigator approached the UK Community Advisory Board (UK-CAB), a network for community HIV treatment advocates, and asked for an opportunity to discuss the trial design at its meetings. He presented the trial design on two occasions and obtained useful feedback that resulted in a number of suggestions being incorporated in the final protocol (e.g. the suggestion to include therapeutic drug monitoring of PI levels at the first visit following randomisation in the PI-mono group).

At these meetings and in follow-up correspondence with UK-CAB, the chief investigator explained about the roles of the Trial Steering Committee (TSC) and the IDMC and requested that UK-CAB provide a representative on each of these committees. A lay summary of the roles was produced as well as a description of the attributes that would be desired in those selected. UK-CAB organised an election process and a nominee for each of the two committees was selected.

The IDMC community representative attended all of the IDMC meetings and contributed to the discussion of the blinded data throughout the course of the trial.

The TSC community representative attended all of the TSC meetings and provided input into the final study protocol and all subsequent key decisions made during the course of the trial, including the approval of the study amendments, decisions on the viability of substudies, the decision to increase the sample size and include more sites in the UK and discussions around classification of end points in the final analysis. The TSC representative also fed back to the chief investigator any concerns that were circulating in the community or any community discussions (usually not directly related to the trial) about PI monotherapy that might impact on the trial and which needed to be addressed.

In parallel with engagement with UK-CAB and its nominated representatives, the trial team engaged with the African Eye Trust, a community group focused on the support of African HIV-positive patients, who represent a substantial proportion of the infected community in the UK. This community group organised workshops at regional sites that talked generally about clinical trials but which also specifically mentioned the PIVOT trial design and the opportunity that it presented for members of the community to participate in a trial. The trial was also featured in an article in the *African Eye Voice* magazine. Members of the African Eye Trust also helped patients who expressed an interest in the trial to understand the trial requirements and processes. This engagement likely contributed to the substantial representation of African patients in the trial (see *Chapter 3*), which is unusual for HIV trials conducted in the UK, Europe and North America, where enrolment tends to be dominated by white men who have sex with men.

Once the trial was complete, all participants were invited to hear about the results at a meeting that immediately followed (in the same afternoon) the results meeting for investigators. The study team, as well as several site investigators, were available to help patients interpret the findings and to answer questions about the study. This meeting was held before the formal release of the results at a major international HIV conference the following week. Participants provided very positive feedback and were highly appreciative of the opportunity to hear and discuss the results before their release at the conference.

Chapter 3 Results of the clinical trial

Trial recruitment

Recruitment to the trial commenced on 4 November 2008 with a target of 400 patients. In July 2009 the sample size was increased to 570 patients as emerging data from other studies[22,25] indicated that event rates for the primary end point would likely be lower than first estimated. Recruitment ended on 28 July 2010 with 587 participants recruited from 43 sites across the UK (*Figure 1*). Study visits ended on 1 November 2013.

Baseline characteristics of the study participants

Participant characteristics were similar between groups at baseline (*Table 2*). The median time on previous ART was 4 years and 53% were on a NNRTI-containing regimen at baseline.

Trial follow-up and withdrawal

The median duration of trial follow-up was 44 months (maximum 59 months); 1% died and 2.7% were withdrawn/lost to follow-up before the end of the trial (*Figure 2*).

Treatment and adherence

In the PI-mono group, the initial choice of PI was DRV (80%), LPV (14%) or another boosted PI (6%); 58% were still taking PI monotherapy at the end of the trial (23% reintroduced combination therapy for VL rebound, 4% reintroduced combination therapy for VL rebound not meeting protocol criteria,

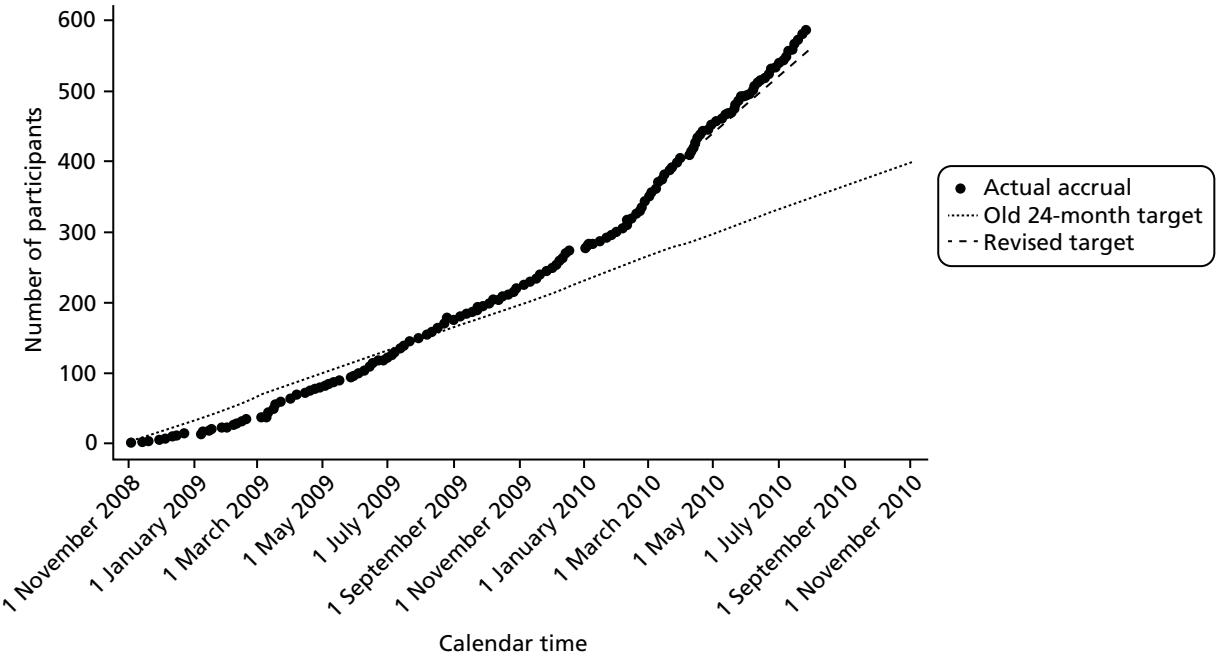

FIGURE 1 Trial recruitment.

TABLE 2 Baseline characteristics

Characteristics	OT (*n* = 291)	PI-mono (*n* = 296)	Total (*n* = 587)
Demographic and clinical characteristics			
Age (years)			
Median (IQR)	43 (37–49)	45 (39–50)	44 (38–49)
Range	23–75	23–67	23–75
Mode of infection, *n* (%)			
MSM	175 (60)	176 (59)	351 (60)
Heterosexual	108 (37)	108 (36)	216 (37)
Other	8 (3)	12 (4)	20 (3)
Female, *n* (%)	64 (22)	73 (25)	137 (23)
Ethnicity, *n* (%)			
White	206 (71)	195 (66)	401 (68)
Black	73 (25)	90 (30)	163 (28)
Other	12 (4)	11 (4)	23 (4)
HCV antibody positive, *n* (%)	7 (2)	14 (5)	21 (4)
HIV disease status			
Previous AIDS-defining illness, *n* (%)	59 (20)	57 (19)	116 (20)
Nadir CD4 cells/mm^3, median (IQR)	181 (90–258)	170 (80–239)	178 (86–250)
Baseline CD4 cells/mm^3, median (IQR)	512 (386–658)	516 (402–713)	513 (392–682)
Baseline HIV VL undetectable, *n* (%)	276 (95)	279 (94)	555 (95)
Duration of VL undetectable (months), median (IQR)	36 (17–62)	38 (22–66)	37 (20–63)
ART history			
Years since ART start, median (IQR)	3.9 (2.0–6.4)	4.2 (2.4–6.9)	4.0 (2.2–6.7)
Number of drugs ever received, median (IQR)	5 (3–6)	4 (3–6)	4 (3–6)
NNRTI at entry, *n* (%)			
Any	157 (54)	157 (53)	314 (53)
Efavirenz	115 (40)	115 (39)	230 (39)
Nevirapine	42 (14)	39 (13)	81 (14)
Etravirine	0 (0)	3 (1)	3 (1)
PI at entry, *n* (%)			
Any	134 (46)	139 (47)	273 (47)
Atazanavir	59 (20)	59 (20)	118 (20)
LPV	28 (10)	49 (17)	77 (13)
DRV	24 (8)	13 (4)	37 (6)
Saquinavir	16 (5)	15 (5)	31 (5)
Fosamprenavir	7 (2)	3 (1)	10 (2)
NRTIs at entry, *n* (%)			
Any	291 (100)	296 (100)	587 (100)
Emtricitabine/tenofovir	190 (65)	180 (61)	370 (63)
Lamivudine/abacavir	80 (27)	82 (28)	162 (28)
Other	21 (7)	34 (11)	55 (9)

IQR, interquartile range; MSM, men who have sex with men.

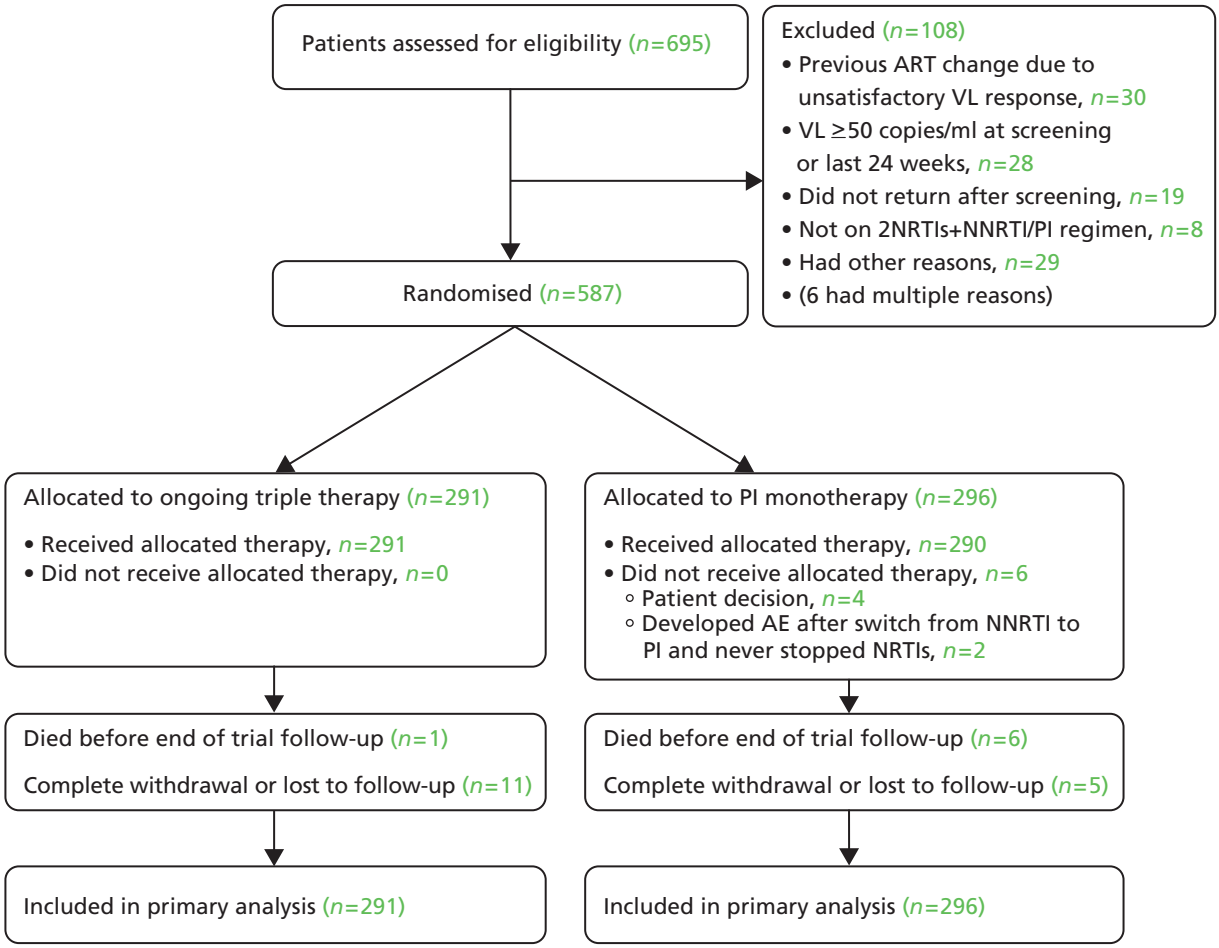

FIGURE 2 Consolidated Standards of Reporting Trials (CONSORT) diagram.

5% reintroduced combination therapy for toxicity, 7% reintroduced combination therapy for other reasons/unknown and 2% never started monotherapy). Overall, 72% of follow-up time was spent on monotherapy. Self-reported adherence to study medication was high; across all visits, 93% of participants in the OT group and 92% of participants in the PI-mono group reported not missing any ART doses in the last 2 weeks ($p = 0.51$).

Virological rebound and resuppression

One or more episodes of confirmed VL rebound were observed in eight patients (Kaplan–Meier estimate 3.2%) in the OT group and 95 patients (35.0%) in the PI-mono group (absolute risk difference 31.8%, 95% CI 24.6% to 39.0%; $p < 0.001$). The rate of rebound while on monotherapy was highest in the first year (24 per 100 person-years vs. 6 per 100 person-years thereafter; *Figure 3*).

There was no difference in the rate of rebound by PI in the PI-mono group [14 (95% CI 11 to 17), 8 (95% CI 4 to 17) and 12 (95% CI 5 to 27) rebounds per 100 person-years for DRV, LPV, and other PIs respectively; $p = 0.52$ for overall comparison between groups]. The median peak VL at first episode of rebound on monotherapy was 526 copies/ml; of the 91 patients with subsequent VL tests, 22 (24%) resuppressed spontaneously and 69 (76%) resuppressed a median of 3.5 weeks after changing ART.

Figure 4 shows the time to first VL below 50 copies/ml (mid-point between the last test with a VL above 50 copies/ml and the first test with a VL below 50 copies/ml) for patients at the time of first rebound who were taking PI monotherapy. Outcomes by type of treatment switch are shown in *Figure 5*.

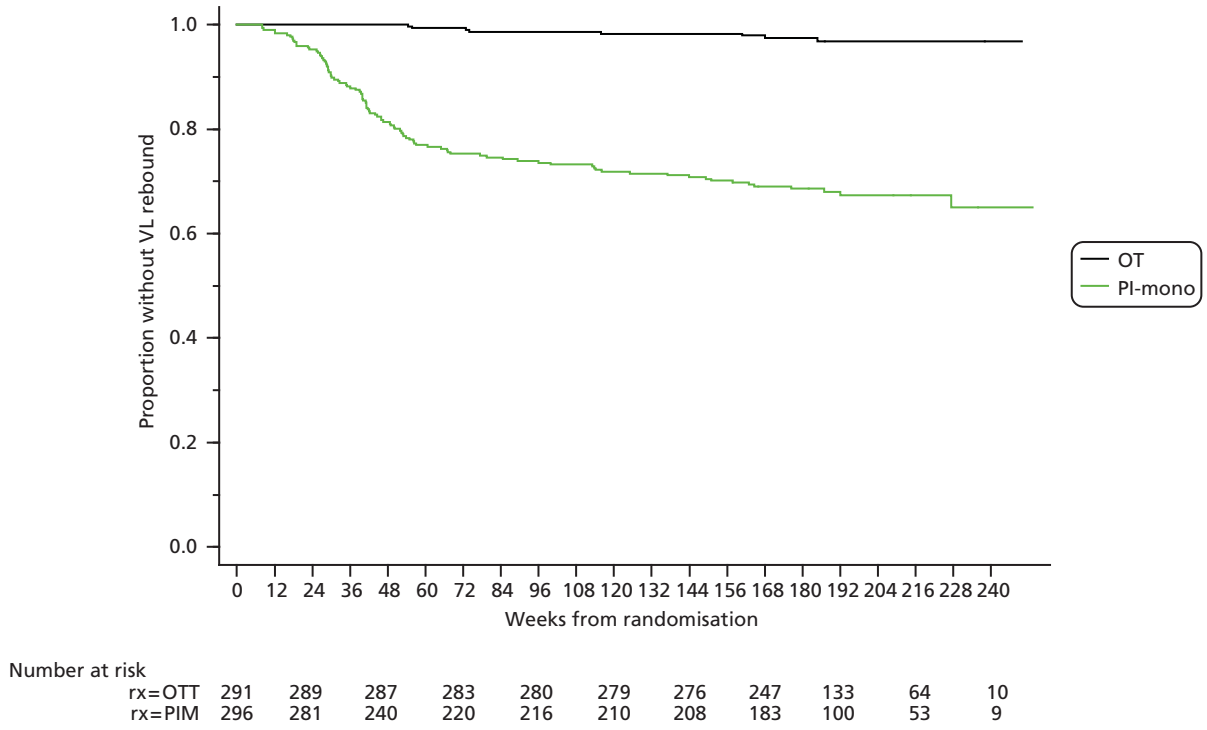

FIGURE 3 Time to virological rebound.

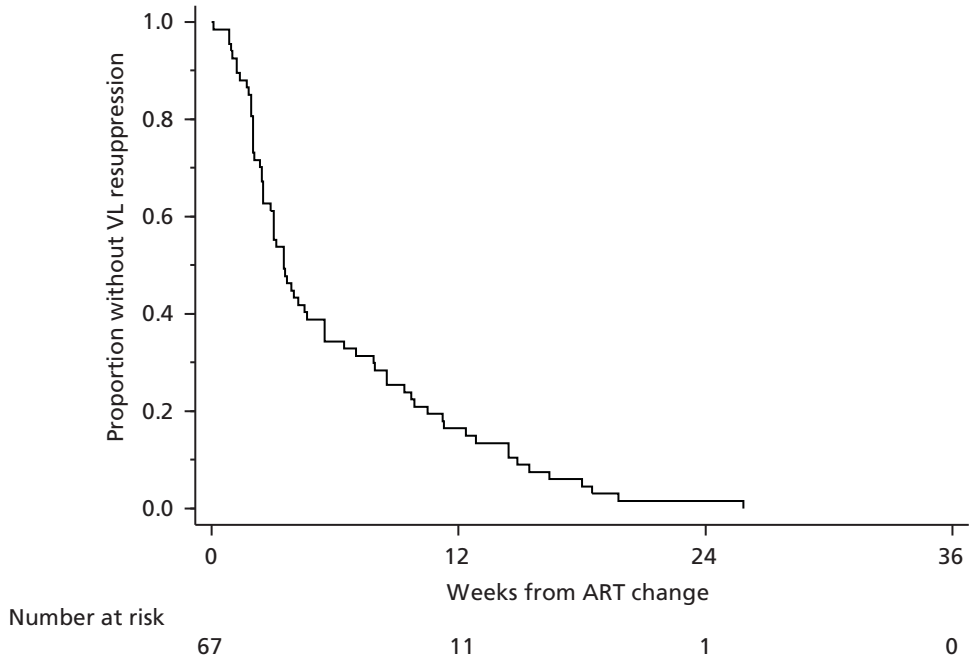

FIGURE 4 Time to VL resuppression following change of ART in the PI-mono group.

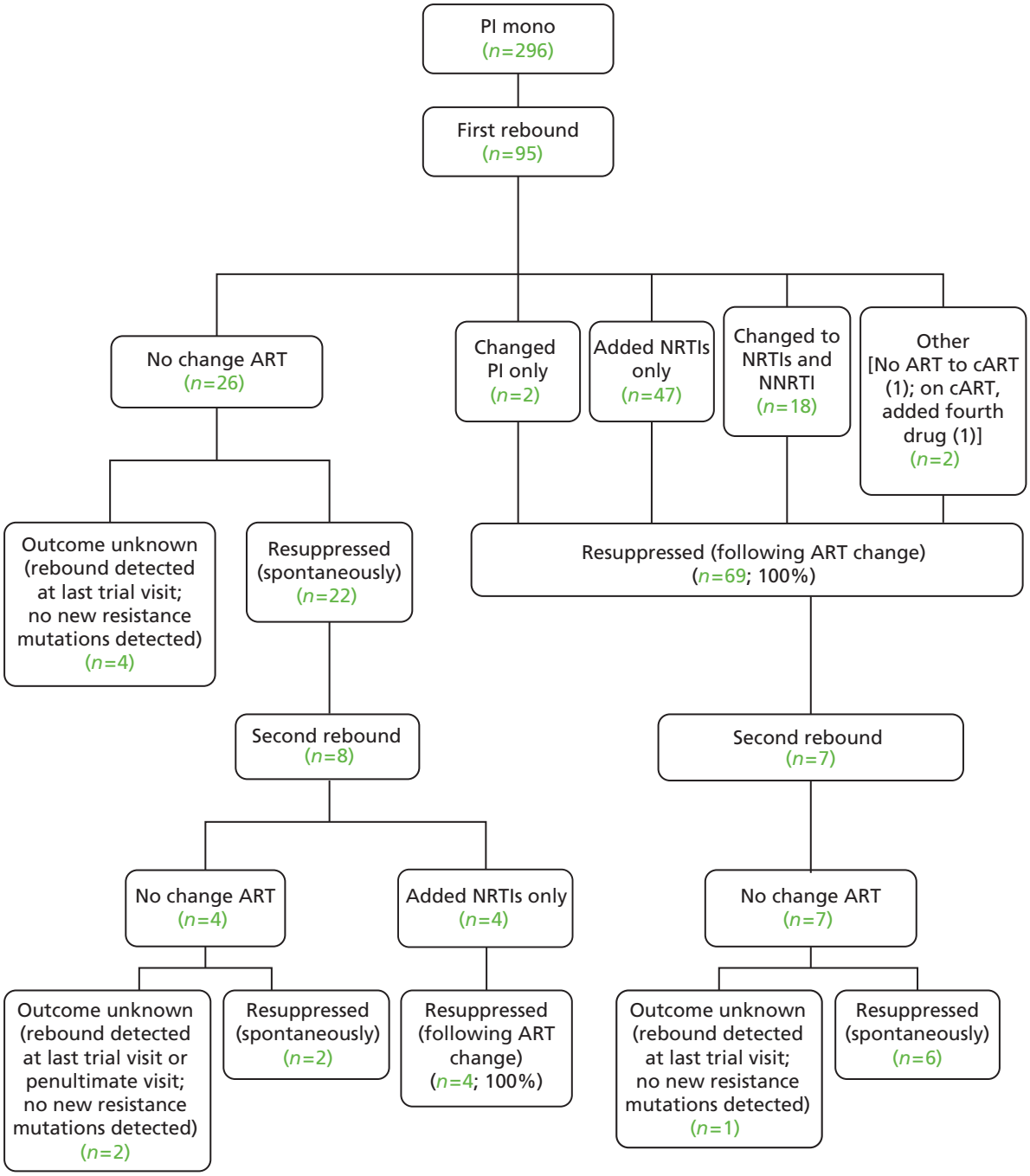

FIGURE 5 Outcome of VL rebound episodes in the PI-mono group.

Resistance and loss of future drug options

The proportion of patients with loss of future drug options at 3 years, the primary outcome, was 0.7% in the OT group and 2.1% in the PI-mono group [difference 1.4% (–0.4% to +3.4%); non-inferiority criterion met; *Table 3*]. PI-mono was also non-inferior in prespecified secondary analyses including the loss of drug options during the full trial follow-up period and excluding loss of options attributed to mutations likely to be archived (as described in the following paragraph).

One participant on atazanavir monotherapy developed the I50L mutation (as a mixture with wild type), conferring high-level atazanavir resistance. An isolated L90M mutation was detected in two patients on DRV monotherapy; both resuppressed with the reintroduction of NRTIs. This mutation, possibly archived, does not affect DRV sensitivity but confers resistance to saquinavir and thus met the end point definition. NRTI or NNRTI mutations were detected in three patients in the PI-mono group, likely archived from previous treatment. In the OT group, three patients had loss of future drug options to drug classes that they were taking and one, taking a PI-based regimen, had NNRTI mutations that were likely archived (*Tables 3* and *4*).

Serious drug- or disease-related complications

There were no differences in serious drug- or disease-related complications (death, AIDS-defining illness, serious non-AIDS-defining illness) (*Tables 5–7*). Causes of death (one in the OT group, six in the PI-mono group) were diverse and none was considered to be related to the treatment strategy (see *Table 6*).

TABLE 3 Primary outcome: loss of future drug options – summary results

Loss of future drug options[a]	OT[b]	PI-mono[b]	PI-mono – OT[c]
At 36 months, *n* (%)	$2^{1,2}$ (0.7)	$6^{5–10}$ (2.1)	1.4% (–0.4% to 3.4%)
At the end of the trial, *n* (%)	$4^{1–4}$ (1.8)	$6^{5–10}$ (2.1)	0.2% (–2.5% to 2.6%)
At the end of the trial, limited to drug classes given during the trial (excluding likely archived resistance), *n* (%)	$3^{1–3}$ (1.5)	$3^{5–7}$ (1.0)	–0.4% (–2.1% to 1.4%)

3TC, lamivudine; ABC, abacavir; ATV, atazanavir; EFV, efavirenz; ETV etravirine; FPV fosamprenavir; FTC, emtricitabine; NVP nevirapine; RPV, rilpivirine; SQV, saquinavir; TDF, tenofovir; TPV tipranavir; ZDV, zidovudine.

a Loss of future drug options is defined as new intermediate-/high-level resistance to one or more drugs in contemporary use (treatment options listed in the British HIV Association (BHIVA) 2012 treatment guidelines,[63] with SQV added) to which the patient's virus was considered to be sensitive at trial entry.

b Numbers in superscript refer to individual patients meeting the primary end point (more detail provided in *Table 4*): (1) OT group, received ABC, 3TC, ATV; detected 118I, 179D, 184V, 84V; lost 3TC, FTC, SQV, FPV, TPV; (2) OT group, received TDF, FTC, RPV; detected 100I, 103N, 184V, 71V; lost 3TC, FTC, NVP, EFV, ETV, RPV; (3) OT group, received TDF, FTC, ETV, NVP, ETV; detected 184V/I, 65R, 138A, 181C, 221Y, 230L; lost 3TC, FTC, ABC, TDF, NVP, EFV, ETV, RPV; (4) OT group, received TDF, FTC, DRV; detected 106A; lost NVP, EFV (likely archived resistance); (5) PI-mono group, received ATV; detected 20T, 50L/I, 71T; lost ATV; (6) PI-mono group, received DRV; detected 90M; lost SQV (possibly archived resistance); (7) PI-mono group, received DRV; detected 90M; lost SQV (possibly archived resistance); (8) PI-mono group, received DRV; detected 103N; lost NVP, EFV (likely archived resistance); (9) PI-mono group, received DRV; detected 103N; lost NVP, EFV (likely archived resistance); (10) PI-mono group, received DRV; detected 41L, 215D; lost ZDV (likely archived resistance).

c The absolute difference between the groups was estimated using Kaplan–Meier analysis, with the 95% CI (two-sided) derived using bootstrap methods.

TABLE 4 Detailed treatment history, VL rebound and resistance test results in cases meeting the definition of the primary end point, loss of future drug options[a]

	Cumulative ART exposure before trial entry		Time of resistance test (trial week)[b]	Cumulative ART exposure during the trial[c]		VL (copies/ml) at time of resistance test	Drug-resistance mutations present[d]		Drugs with reduced susceptibility[e]		
Patient	NRTI, NNRTI	PI		NRTI, NNRTI,II	PI		RT	PRO	NRTI	NNRTI	PI
OT group											
1	ZDV, 3TC, NVP, ABC	ATV	–89	–	–	–	118I, 179D	–	–	–	–
			70	ABC, 3TC	ATV	33,300	118I, 179D, 184V	84V	3TC^{H}, FTC^{H}	–	SQV^{H}, TPV^{I}, ATV^{I}, FPV^{H}
			185	TDF, FTC, RAL (3TC, ABC)	DRV (ATV)	4100	118I, 179D	–	–	–	–
2	d4T, TDF, EFV, FTC	DRV	–286	–	–	–	–	71V	–	–	–
			193	TDF, FTC, RPV	(DRV)	1500	100I, 103N, 184V	71V	3TC^{H}, FTC^{H}	NVP^{H}, EFV^{H}, ETV^{I}, RPV^{I}	–
3	ddI, 3TC, EFV, FTC, TDF		161	TDF, FTC, ETV (EFV, NVP)	(DRV)	60	138A, 184V/I	–	3TC^{H}, FTC^{H}	–	–
			167	TDF, FTC, ETV (EFV, NVP)	(DRV)	5400	65R, 138A, 181C, 184V/I, 221Y, 230L	–	3TC^{H}, FTC^{H}, ABC^{H}, TDF^{I}	NVP^{H}, EFV^{H}, ETV^{H}, RPV^{H}	–
4	3TC, ABC	LPV, SQV	–179	–	–	–	–	–	–	–	–
			51	TDF, FTC	DRV	2300	106A	–	–	NVP^{H}, EFV^{I}	–

continued

TABLE 4 Detailed treatment history, VL rebound and resistance test results in cases meeting the definition of the primary end point, loss of future drug options[a] (*continued*)

Patient	Cumulative ART exposure before trial entry		Time of resistance test (trial week)[b]	Cumulative ART exposure during the trial[c]		VL (copies/ml) at time of resistance test	Drug-resistance mutations present[d]		Drugs with reduced susceptibility[e]		
	NRTI, NNRTI	PI		NRTI, NNRTI,II	PI		RT	PRO	NRTI	NNRTI	PI
PI-mono group											
5	FTC, TDF, EFV	–	–165	–	–	–	–	71T	–	–	–
			48	–	ATV	23,400	–	20T, 50L/I, 71T	–	–	ATV[H]
			57	–	ATV	3300	–	20T, 71T	–	–	–
			61	–	ATV	2400	–	71T	–	–	–
6	ZDV, 3TC, ABC, EFV	LPV	155	–	DRV	200	–	90M	–	–	SQV[I]
7	FTC, TDF, EFV	–	73	–	DRV	300	–	71I, 90M	–	–	SQV[I]
8	3TC, ABC, EFV	–	82	–	DRV	<20	103N	–	–	NVP[H], EFV[H]	–
9	ZDV, 3TC, FTC, TDF, NVP	SQV	–290	–	–	–	–	11I	–	–	–
			83	–	DRV	1100	103N	–	–	NVP[H], EFV[H]	–
10	ZDV, 3TC	LPV	17	–	DRV	300	41L, 215D	–	ZDV[I]	–	–

3TC, lamivudine; ABC, abacavir; ATV, atazanavir; d4T, stavudine; ddI, didanosine; EFV, efavirenz; ETV, etravirine; FPV, fosamprenavir; FTC, emtricitabine; NVP, nevirapine; PRO, protease; RAL, raltegravir; RPV, rilpivirine; RT, reverse transcriptase; SQV, saquinavir; TDF, tenofovir; TPV tipranavir; ZDV, zidovudine.

a Drugs used for <28 days are not reported.

b A negative value refers to the timing of a pre-trial resistance test relative to randomisation (usually obtained before the start of ART if performed).

c Shown is the cumulative drug exposure between randomisation and the time of performing the resistance test. PI-mono patients continued NRTIs for the first 14 days after randomisation (drugs not shown). Drugs taken during the trial but discontinued prior to the resistance test are shown in parentheses.

d Drug-resistance mutations limited to those used in the Stanford algorithm.[57]

e Drug susceptibility determined from the Stanford algorithm.[57] List limited to drugs that are included as treatment options in the British HIV Association (BHIVA) 2012 treatment guidelines, with the addition of SQV. Superscript denotes the level of predicted resistance: I = intermediate, H = high.

TABLE 5 Safety outcomes summary table

Serious drug- or disease-related complications	OT[a] ($n = 291$)	PI-mono[a] ($n = 296$)	Difference (95% CI) (%)[b]	*p*-value
Total, *n* (%)	8 (2.8)	15 (5.1)	2.3 (–0.8 to 5.4)	0.15
Death, *n* (%)	1 (0.3)	6 (2)	1.7 (–0.3 to 3.6)	0.12
AIDS-defining event, *n* (%)	1 (0.3)	1 (0.3)	0.0 (–1.3 to 1.3)	1
Serious non-AIDS-defining event, *n* (%)	7 (2.4)	12 (4.1)	1.6 (–1.2 to 4.5)	0.26

a Number (percentage) of patients experiencing the specified event during the entire trial follow-up period. *p*-Values are from chi-squared or exact tests.
b Risk difference: PI-mono – OT.

TABLE 6 Causes of death, risk factors and HIV disease status during trial follow-up prior to the presentation of the terminal condition

Patient (group)	Cause of death (week of presentation of terminal condition)	Clinical history and risk factors	HIV disease status from trial entry to presentation of terminal condition
1 (OT)	Metastatic adenocarcinoma, probable lung origin (week 20)	58-year-old male; 40 pack per year history of smoking; presented with a right thigh mass; mediastinal and adrenal mass on CT	CD4 525 cells/mm^2 at baseline; VL suppressed from randomisation to presentation of the terminal condition
2 (PI-mono)	Trauma, presumed suicide (week 17)	47-year-old male; no history of depression	CD4 215 cells/mm^2 at baseline; VL suppressed from randomisation to death
3 (PI-mono)	Pulmonary embolism (week 51)	40-year-old female; hospitalisation for encephalitis (weeks 40–50); pulmonary embolism secondary to deep-vein thrombosis	CD4 333 cells/mm^2 at baseline; VL rebound week 36 because of non-adherence; resuppressed partially with reintroduction of combination therapy
4 (PI-mono)	Breast carcinoma, recurrent (week 7)	54-year-old female; angiosarcoma of the breast 2 years before study entry treated by mastectomy	CD4 550 cells/mm^2 at baseline; VL suppressed from randomisation to presentation of the terminal condition
5 (PI-mono)	Small-cell lung carcinoma (week 178)	59-year-old male; smoker for 30 years; presented with headache; lung mass on CT, biopsy showed small-cell carcinoma of the lung	CD4 208 cells/mm^2 at baseline; VL suppressed from randomisation to presentation of the terminal condition
6 (PI-mono)	Glioblastoma (week 66)	61-year-old male; non-smoker; presented with headache at week 66; brain mass on CT, biopsy showed high-grade glioblastoma	CD4 468 cells/mm^2 at baseline; VL rebound weeks 25–32 (< 300 copies/ml). Resuppressed with addition of TDF/FTC thereafter
7 (PI-mono)	Anal carcinoma (week 80)	56-year-old male; smoker; anal mass detected; biopsy showed squamous cell carcinoma	CD4 319 cells/mm^2 at baseline; VL rebound weeks 24–43 (max. 815 copies/ml). Resuppressed with addition of TDF/FTC thereafter

CT, computerised (axial) tomography; FTC, emtricitabine; TDF, tenofovir.

TABLE 7 Serious AIDS- and non-AIDS-defining events

Event	OT ($n = 291$)	PI-mono ($n = 296$)
Serious AIDS-defining events		
AIDS encephalopathy		1
Cytomegalovirus colitis	1	
Serious non-AIDS-defining events		
Acute pancreatitis		1
Facial wasting	1	
Myocardial infarction	1	
Renal failure		1
Malignancy	5	10
Anal squamous cell carcinoma		1[a]
CNS (glioblastoma)		1[a]
Hodgkin's disease	1	
Lung (small-cell carcinoma)		1[a]
Metastatic carcinoma (angiosarcoma, unknown primary)	1[a]	1[a]
Prostate cancer	2	1
Renal cell carcinoma		1
Skin carcinoma (various[b])	1	4

a Causing death.
b Basal cell carcinoma (OT, $n = 1$; PI-mono, $n = 1$); carcinoma in situ (PI mono, $n = 2$); squamous cell carcinoma (PI-mono, $n = 1$).

Serious adverse events and grade 3/4 clinical events

The number of serious adverse events (SAEs) overall and by category and the number of SAEs that were considered to be related to ART did not differ between the groups (*Tables 8–10*). However, there were fewer total grade 3 or 4 AEs in the PI-mono group (see *Table 8*), the difference reflecting fewer laboratory events (*Table 11*).

TABLE 8 Serious adverse events and grade 3/4 AEs

Event	OT[a] ($n = 291$)	PI-mono[a] ($n = 296$)	Difference (95% CI) (%)[b]	*p*-value
SAE, *n* (%)	45 (15)	56 (19)	3.5 (–2.6 to 9.6)	0.27
Grade 3/4 AE, *n* (%)	159 (55)	137 (46)	–8.4 (–16.4 to –0.3)	0.043

a Number (percentage) of patients experiencing the event specified at least once during the entire trial follow-up period.
b Risk difference: PT-mono – OT.

TABLE 9 Serious adverse events by category of event

Event	OT ($n = 291$)[a]	PI-mono ($n = 296$)[a]
Total events	61	75
Death	1	6
Life-threatening	4	2
Caused/prolonged hospitalisation	58	67
Disability/incapacity	0	2
Congenital anomaly/birth defect	0	0
Other	4	5

a Number of events in each category.
Note
There is overlap of categories meaning that some events are in more than one category.

TABLE 10 Adverse events that were considered to be related to ART

Event	OT ($n = 291$)[a]	PI-mono ($n = 296$)[a]	Difference (95% CI) (%)	*p*-value[b]
Total	6 (2.1)	3 (1.0)	–1.0 (–3.2 to 1.1)	0.34
Death	0	0		
SAE	2	0		
Grade 3/4 AE	3	3		
SAE plus grade 3/4 AE	1	0		

a Total number (percentage) of patients with any event considered as possibly, probably or definitely related to ART based on independent review at the co-ordinating centre. The numbers of events are shown for the individual categories.
b The *p*-value was calculated for a Fisher's exact test for the proportion of patients affected.

TABLE 11 Grade 3/4 AEs by clinical and laboratory category

Event	OT ($n = 291$)[a]	PI-mono ($n = 296$)[a]	Difference (95% CI) (%)[b]	p-value[c]
Clinical events				
Total	49 (17) [78]	65 (22) [91]	5.1 (–1.3 to 11.5)	0.12
Cardiovascular	8 (3) [11]	7 (2) [7]	–0.4 (–2.9 to 2.2)	0.77
Respiratory	5 (2) [5]	11 (4) [11]	2.0 (–0.6 to 4.6)	0.14
Gastrointestinal	12 (4) [15]	7 (2) [8]	–1.8 (–4.6 to 1.1)	0.23
Hepatic	2 (1) [2]	3 (1) [3]	0.3 (–1.4 to 2.1)	1.00
Renal[d]	2 (1) [2]	3 (1) [3]	0.3 (–1.4 to 2.1)	1.00
CNS[e]	9 (3) [10]	17 (6) [20]	2.7 (–0.7 to 6.0)	0.12
Skin	7 (2) [7]	9 (3) [9]	0.6 (–2.0 to 3.3)	0.64
Other	20 (7) [26]	24 (8) [30]	1.2 (–3.0 to 5.5)	0.57
Laboratory events				
Total	131 (45) [158]	97 (33) [117]	–12.2 (–20.1 to –4.4)	0.002
Phosphate decreased	73 (25)	37 (13)	–12.6 (–18.8 to –6.3)	< 0.001
Bilirubin increased	44 (15)	21 (7)	–8.0 (–13.1 to –3.0)	0.002
Lipids increased	22 (8)	39 (13)	5.6 (0.7 to 10.5)	0.026
Haematological	8 (3)	5 (2)	–1.1 (–3.4 to 1.3)	0.38
Other	7 (2)	11 (4)	1.3 (–1.5 to 4.1)	0.36

a Number (percentage) of patients with a given type of grade 3 or 4 AE and the total number of events in each category. Recurrent laboratory events in the same patient were counted as a single event.
b Absolute differences in the proportions of patients affected in each group.
c p-values were calculated for chi-squared or Fisher's exact tests for the proportion of patients affected.
d Renal events were nephrolithiasis and pyelonephritis in the OT group and renal cell carcinoma, end-stage renal failure (progression of existing chronic renal impairment present at study entry) and acute renal impairment (transient, accompanying episode of pneumonia) in the PI-mono group.
e CNS events were depression and/or suicidal ideation ($n = 4$), anxiety/stress ($n = 2$), headache ($n = 2$), psychosis ($n = 1$) and normal-pressure hydrocephalus ($n = 1$) in the the OT group and depression and/or suicidal ideation ($n = 9$), anxiety/stress ($n = 1$), headache ($n = 2$), myasthenia gravis ($n = 1$), psychosis ($n = 2$), psychiatric symptoms (unspecified) ($n = 1$), meningioma ($n = 1$), glioblastoma ($n = 1$), head injury ($n = 1$) and convulsion ($n = 1$) in the PI-mono group.

Renal toxicity

Fewer patients in the PI-mono group experienced an eGFR of < 60 ml/minute/1.73 m^2 during follow-up (*Table 12*) and there was a trend towards a reduced decline in eGFR in the PI-mono group (*Figure 6*), although the difference at the end of the trial was marginal (see *Table 12*). There was no evidence of serious clinical consequences: the only case of end-stage renal failure occurred in the PI-mono group in a patient with pre-existing chronic renal impairment at trial entry.

Differences in the numbers ever having an eGFR of < 60 ml/minute/1.73 m^2 as well as in the mean change from baseline were similar when values were calculated using the Cockcroft–Gault equation[64] instead of the CKD-EPI formula.[59]

TABLE 12 Number of patients with an eGFR of < 60 ml/minute/1.73 m² during follow-up and mean change in eGFR from baseline to the last visit

Outcome	OT ($n = 291$)	PI-mono ($n = 296$)	Difference (95% CI)[a]	p-value
Estimated GFR < 60 ml/minute/1.73 m², n/N (%)[b]	28/290 (10)	15/296 (5)	–4.6% (–8.8% to –0.4%)	0.033
Mean change (ml/minute/1.73 m²), mean (SE)	–5.13 ± 0.67	–3.83 ± 0.66	1.30 (–0.55 to 3.15)	0.09

a Difference in mean change or risk difference: PI-mono – OT.
b New episodes after baseline.

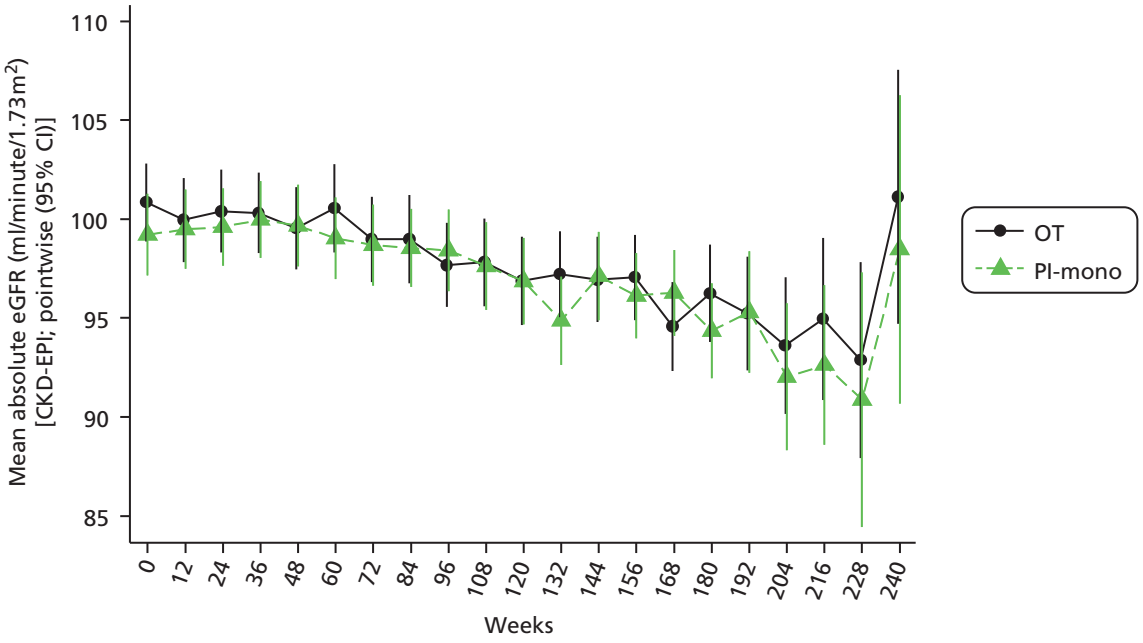

FIGURE 6 Absolute eGFR over time.

Fewer patients in the PI-mono group experienced a phosphate level of < 0.65 mmol/l ($p < 0.001$; see *Table 11*). Patients allocated to the OT group had on average slightly lower serum phosphate levels over the whole follow-up period than patients allocated to the PI-mono group (unadjusted GEE for global difference in mean change, $p = 0.017$; *Figure 7*). There was, however, no significant difference in mean change from baseline to the last available visit, with measurement at or after week 144 (difference PI-mono – OT adjusted for baseline value: +0.02 mmol/l, 95% CI –0.01 to +0.05; t-test $p = 0.48$).

Patients allocated to the OT group had on average a slightly higher urine protein–creatinine ratio over the whole follow-up period than patients allocated to the PI-mono group (unadjusted GEE for global difference in mean change after $\log_{10}$ transformation, $p = 0.021$; *Figure 8*). Patients in the OT group also had a larger urine protein–creatinine ratio at the last available visit with measurement at or after week 144 ($p = 0.026$).

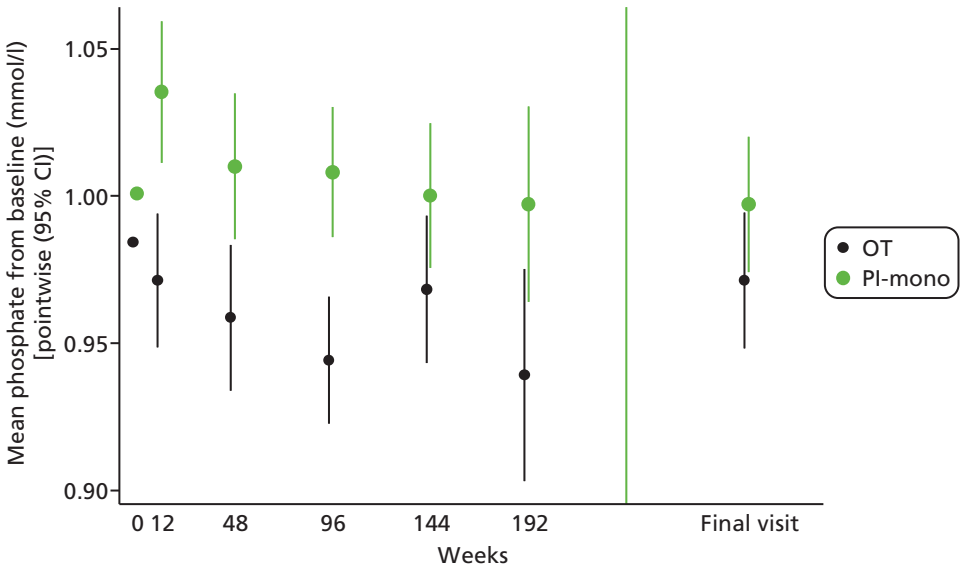

FIGURE 7 Absolute plasma phosphate levels over time.

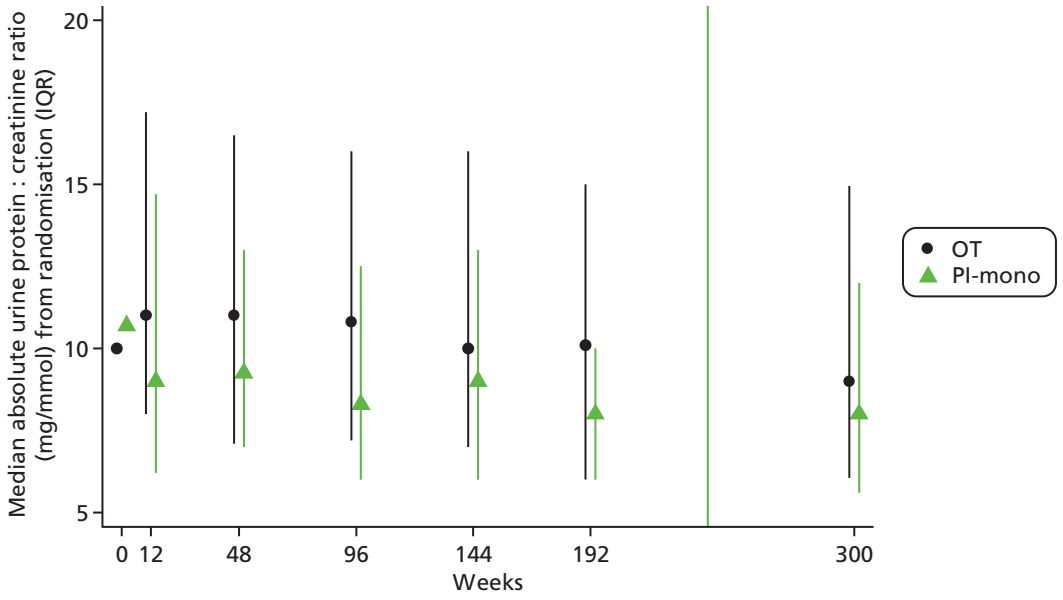

FIGURE 8 Absolute urine protein–creatinine ratio over time. IQR, interquartile range.

In total, 65/271 (24%) in the OT group and 42/270 (16%) in the PI-mono group, respectively, ever had a urine protein–creatinine ratio of > 200 mg/g (difference –8.4%, 95% CI –15.1% to –1.8%; $p = 0.014$), including single increased values (cut-off not prespecified).

Peripheral neuropathy and lipodystrophy

Proportions of patients with symptomatic peripheral neuropathy, facial lipoatrophy and abdominal fat accumulation did not differ between the groups during follow-up (*Table 13* and *Figure 9*).

TABLE 13 Peripheral neuropathy and lipodystrophy outcomes

Outcome	OT ($n = 291$)	PI-mono ($n = 296$)	Difference (95% CI) (%)[a]	p-value
Symptomatic peripheral neuropathy, n/N (%)[b]	44/283 (15.5)	46/289 (15.9)	0.4 (–5.6 to 6.3)	0.90
Facial lipoatrophy, n/N (%)[c]	23/282 (8.2)	35/289 (12.1)	4.0 (–1.0 to 8.9)	0.12
Abdominal fat accumulation, n/N (%)[d]	47/274 (17.2)	57/277 (20.6)	3.4 (–3.1 to 10.0)	0.30

a Absolute difference (PI-mono – OT).
b Symptomatic peripheral neuropathy on one or more of the post-baseline scheduled follow-up assessments (irrespective of status at baseline).
c Facial lipoatrophy present at one or more of the post-baseline scheduled follow-up assessments (irrespective of status at baseline) as assessed by the doctor or nurse.
d Abdominal fat accumulation at the last available assessment compared with baseline (irrespective of status at baseline), self-assessed by the patient.

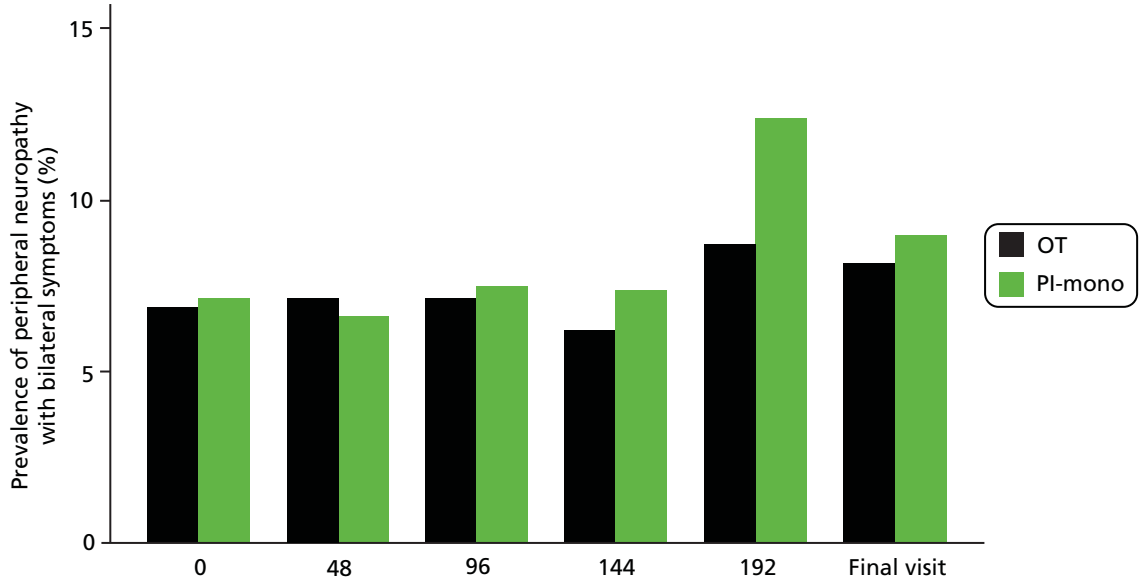

FIGURE 9 Symptomatic peripheral neuropathy prevalence over time.

Cardiovascular disease risk

There was no difference in Framingham risk score[65] between the groups over the whole follow-up period (unadjusted GEE for global difference in mean change, $p = 0.56$) (*Figure 10*). The mean [standard error (SE)] change in risk score for a CVD event over the next 10 years, from baseline to the last available visit, with measurement at or after week 144, was +1.3% (0.3%) and +1.6% (0.3%) in the OT and PI-mono groups, respectively; the difference between the groups adjusted for baseline values was 0.3% (95% CI –0.6% to 1.1%; t-test $p = 0.52$). In total, 9/281 (3%) in the OT group and 16/288 (6%) in the PI-mono group, respectively, ever newly had a CVD risk of > 30% after baseline (difference 2.4%, 95% CI –1.0% to 5.7%; $p = 0.17$).

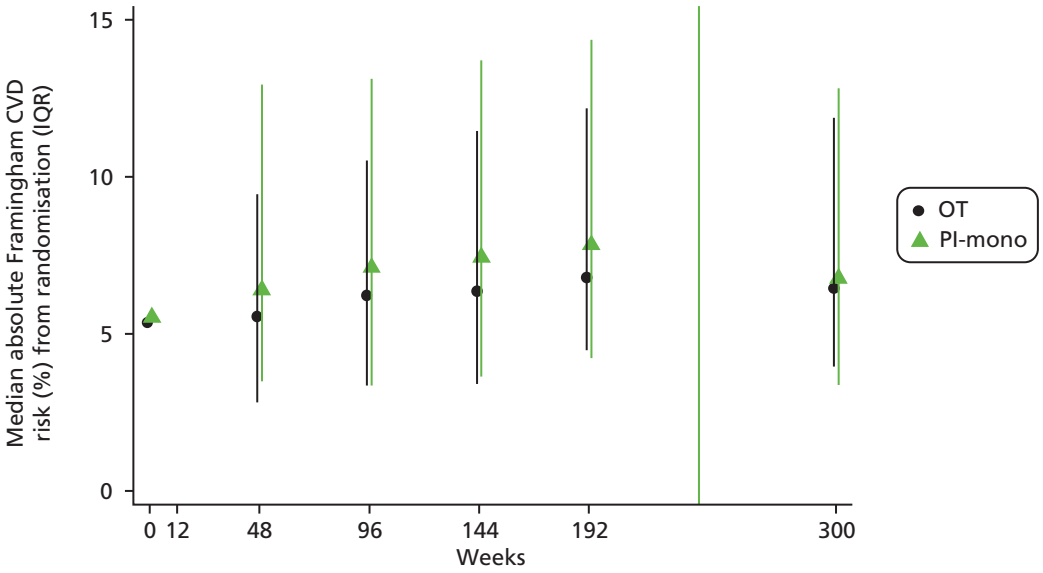

FIGURE 10 Absolute CVD risk over time (estimated using the Framingham equation).

CD4 cell count change

There was no difference in CD4 cell count between groups over the whole follow-up period (unadjusted GEE for global difference in mean change, $p = 0.91$) (*Figure 11*). Mean (SE) change from baseline to the last available visit, with measurement at or after week 144, was +93 (10) cells/mm^3 in the OT group and +109 (9) cells/mm^3 in the PI-mono group; the difference between the groups adjusted for baseline values was +16 (95% CI –11 to +42) cells/mm^3 (*t*-test $p = 0.30$).

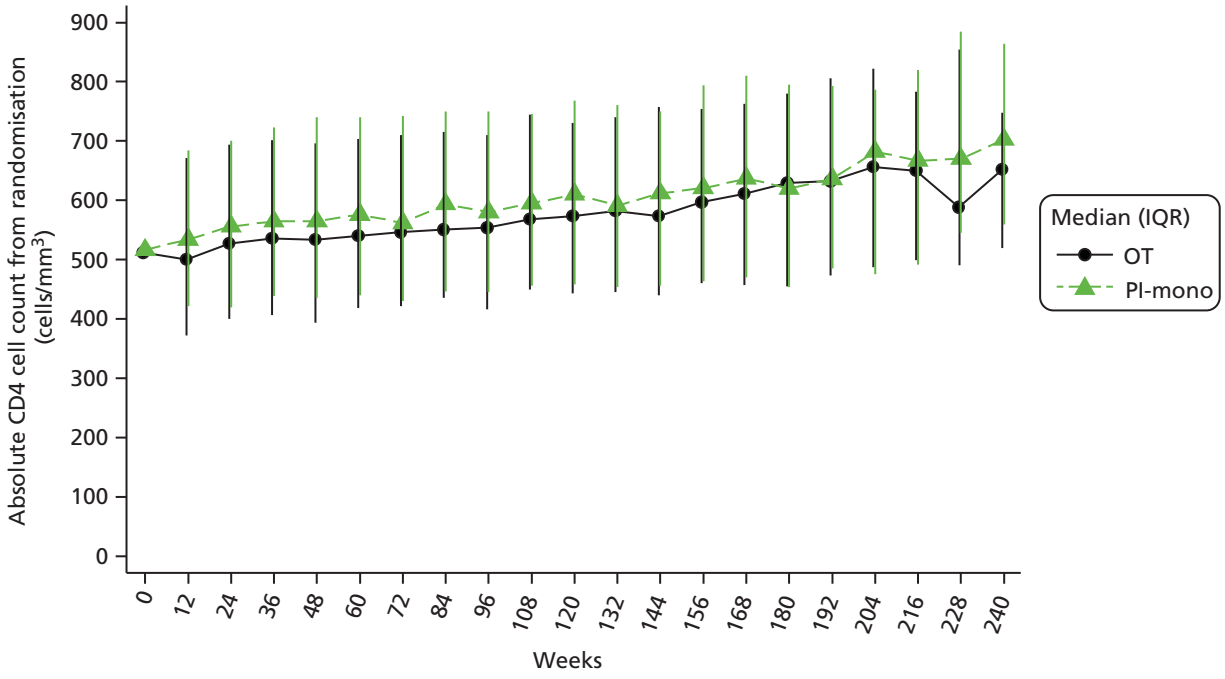

FIGURE 11 Absolute CD4 cell count over time.

Neurocognitive function

There was no difference between the groups in the change in mean NPZ-5 score on the neurocognitive function tests (*Figures 12* and *13*). The mean (SE) change from baseline to the last available visit, with measurement at or after week 144, was +0.53 ± 0.04 and +0.52 ± 0.04 in the OT and PI-mono groups, respectively; the difference between the groups adjusted for baseline value was –0.01 (95% CI –0.11 to 0.09; *t*-test $p = 0.94$).

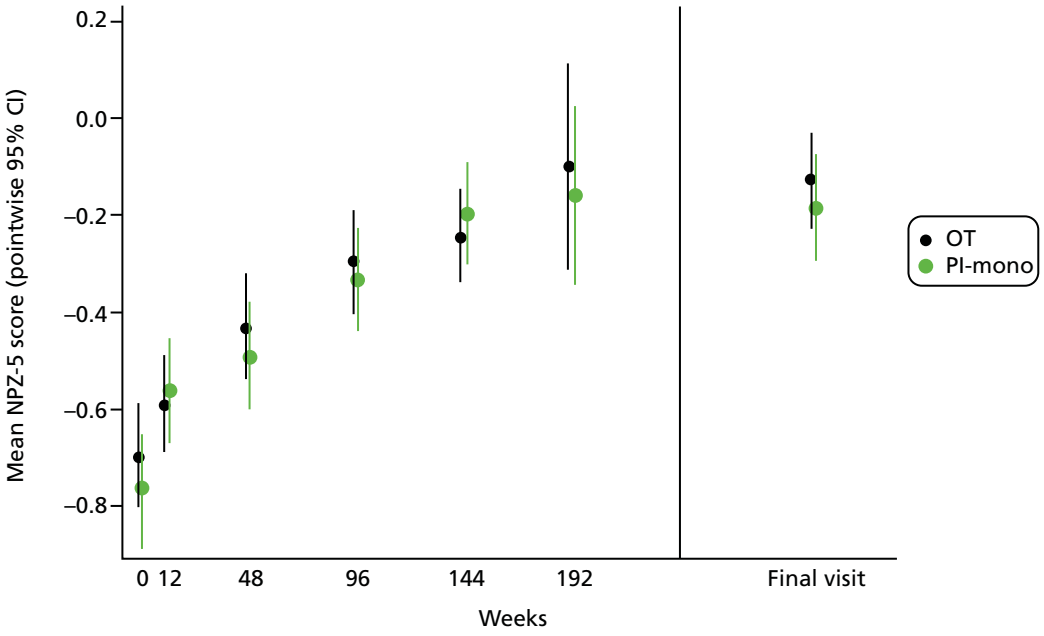

FIGURE 12 Absolute NPZ-5 score over time.

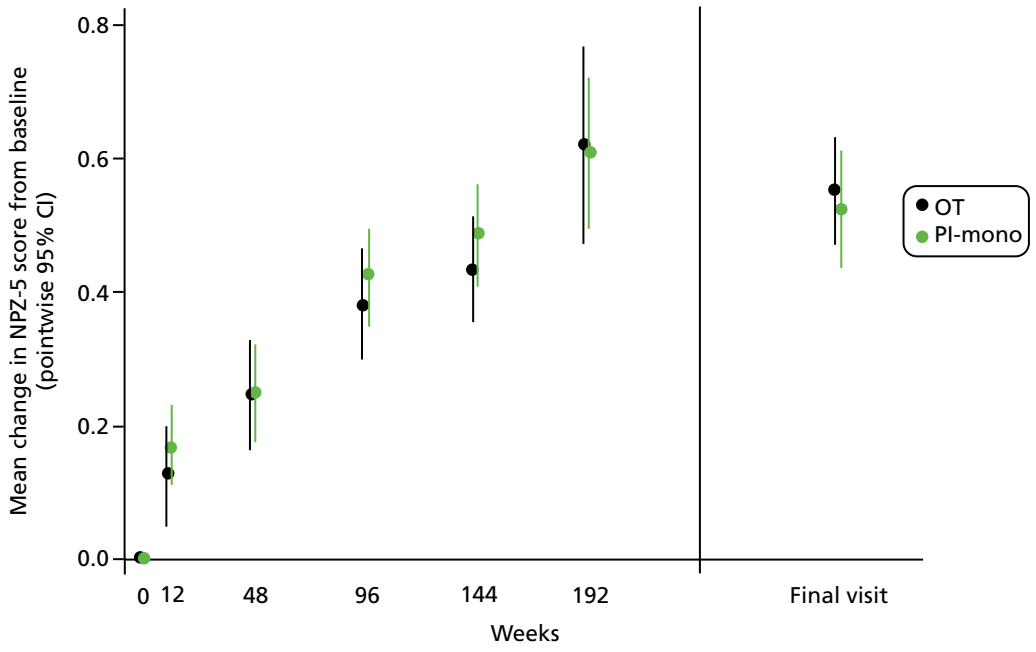

FIGURE 13 Change in NPZ-5 score from baseline.

Quality of life

Changes in the mental and physical health summary scores from baseline to the last study visit were calculated from the responses on the MOS-HIV questionnaire, with imputation of missing data on individual subscales. Changes from baseline were relatively small in both groups and there was no significant difference between the groups (*Table 14*).

TABLE 14 Quality of life: MOS-HIV questionnaire

Quality of life, summary score	OT ($n = 291$)	PI-mono ($n = 296$)	Difference (95% CI)[a]	*p*-value
Mental health, mean change	–0.75 ± 0.57	–1.82 ± 0.54	–1.07 (–2.61 to 0.47)	0.17
Physical health, mean change	–0.76 ± 0.53	–1.17 ± 0.46	–0.41 (–1.79 to 0.98)	0.56

a Difference in mean change: PI-mono – OT.

Chapter 4 Health economics analysis

Outline of the analysis

The objective of the health economics analysis was to investigate the cost-effectiveness of the strategy of switching to PI monotherapy compared with continuing triple therapy in HIV-1-infected patients. The cost-effectiveness analysis considered costs from a NHS perspective (2012 GBP) and health outcomes in terms of quality-adjusted life-years (QALYs) for each treatment group from the PIVOT trial. The base-case analysis was a within-trial analysis and had a 3-year (156-week) time horizon. Secondary analyses modelled lifetime costs and outcomes. All analyses were performed using individual patient-level data on resource use and HRQoL from the PIVOT trial. *Table 15* provides a description of the data collected for the economic evaluation.

Missing data on costs and QALYs were handled using multiple imputation (MI) and regression analysis was used to adjust for baseline covariates. When one option generated additional mean QALYs at a higher mean cost, comparative results were presented as incremental cost-effectiveness ratios (ICERs) by dividing the difference in mean costs by the difference in mean QALYs.[66] The cost-effectiveness of PI-mono was assessed by comparing ICERs to the cost-effectiveness threshold range of £20,000–30,000 per QALY defined by the National Institute for Health and Care Excellence (NICE).[67] All analyses were conducted on an intention-to-treat basis. All costs and QALYs accrued beyond the first year were discounted at an annual rate of 3.5%.[67]

TABLE 15 Data collected for the economic evaluation during the PIVOT trial

Category	Description of data collected	Time points
HRQoL	The European Quality of Life-5 Dimensions 3 Level (EQ-5D-3L) health questionnaire	Baseline and every 12 weeks
ART drug costs	Generic names of ART drugs used as well as dosage, quantity and duration of usage	Every 12 weeks
Cost of visits to HIV clinics	Scheduled visits to HIV clinics every 12 weeks in the PI-mono group and an additional scheduled appointment within the first 12 weeks after initiation of monotherapy (frequency considered necessary for routine clinical care on monotherapy)	Every 12 weeks
	Scheduled visits every 24 weeks in the OT group (frequency considered necessary for routine clinical care on triple therapy)	
	Additional unscheduled visits for both groups	
	Includes the cost of usual laboratory tests and additional resistance tests in the PI-mono group	
Cost of hospital services	Visits to non-HIV outpatient clinics or accident and emergency departments	Every 12 weeks
	Inpatient admissions, including length of stay and reason for admission	
Primary care costs	Visits to general practitioners	Every 12 weeks
Trial protocol-driven costs	Measurement of PI concentration in the PI-mono group, required by the trial protocol	Every 12 weeks
	Visits to HIV clinics that are not expected to be part of routine clinical practice, required by the trial protocol	
	Neurocognitive testing, required by the trial protocol	
Cost of concomitant drugs	Generic names of cholesterol-lowering agents used as well as dosage, quantity and duration of usage	Every 12 weeks

Health-care resource usage

Data on resource use were collected at scheduled visits every 12 weeks. In addition to the scheduled visits every 12 weeks, which patients in both trial arms attended, two additional visits were scheduled at weeks 4 and 8 for the PI-mono group. The recording of resource use was based on patients' recollections since the last visit. As patients were asked to recall their use of health-care resources since the last visit it was assumed that visits that followed one or more omitted visits captured all of the use since the last recorded visit. The use of the following types of resources was recorded: ART use, HIV clinic visits, visits to accident and emergency or non-HIV outpatient clinics, general practitioner (GP) visits, hospital inpatient stays and use of concomitant drugs. The use of ART was recorded by clinical staff, whereas the length of any interruptions in ART treatment was based on the patients' own recollections. Concomitant drugs included all cholesterol-lowering agents as the use of these was expected to differ a priori.[68] The patients attending the scheduled visit at week 4 post randomisation were assumed to have their PI drug concentration measured, as per protocol. No further PI drug concentration measurements were assumed to be performed. No attempts were made to distinguish visits that were HIV related from those that were not. In both groups the costs of all visits were included in the calculations. The total resource consumption among the complete cases is summarised in *Table 16* along with the corresponding unit costs.

TABLE 16 Use of health-care resources within 3 years' follow-up for complete cases

	PI-mono ($n = 266$)			OT ($n = 254$)			
Resource type	Mean (SD)	Median (IQR)	Used by, *n* (%)	Mean (SD)	Median (IQR)	Used by, *n* (%)	Unit cost and source[a]
ART drug use at the 3-year follow-up visit							
Monotherapy			162 (60.9)			4 (1.6)	Various[69,70]
Any triple therapy use			104 (39.1)			250 (98.4)	Various[69,70]
No use			0 (0)			0 (0)	£0
Routine HIV clinic visits	16.60 (3.74)	15 (4)	266 (100)	8.31 (3.9)	7 (3)	254 (100)	PI-mono: £411.81;[71,CA] OT: £404[71]
Primary care							
GP visits	6.24 (6.16)	5 (7)	244 (91.7)	6.06 (6.06)	4.75 (6)	234 (92.1)	£53[72]
Hospital services							
Outpatient clinic or A&E visits	3.7 (5.39)	2 (5)	188 (70.7)	4.49 (7.19)	2 (4)	194 (76.4)	£106.20[71]
Inpatient admissions	0.368 (0.83)	0 (0)	60 (22.6)	0.311 (0.79)	0 (0)	50 (19.7)	Various[71]
Trial protocol-driven resource use							
Neurocognitive testing	3.81 (0.56)	4 (0)	265 (99.6)	3.82 (0.58)	4 (0)	252 (99.2)	£32.94[72–75]
PI drug concentration measurements	0.974 (0.16)	1 (0)	259 (97.4)	0 (0)	0 (0)	0 (0)	£60[CA]
Non-routine HIV clinic visits	0.98 (0.24)	1 (0)	255 (95.9)	6.69 (0.67)	7 (0)	254 (100)	PIM: £411.81;[71,CA] OT: £404[71]
Concomitant drug use at the 3-year follow-up visit							
Cholesterol-lowering agents			59 (22.2)			35 (13.8)	Various[70]

A&E, accident and emergency; CA, clinical advice; IQR, interquartile range.
a The term 'various' indicates that a variety of prices was used; rather than listing them all, the source from which they were drawn is presented.

Costs

Resource use estimates were obtained from the PIVOT trial and unit costs were obtained from routinely published national cost sources: the *British National Formulary* (BNF),[70] the Department of Health's Commercial Medicines Unit's Electronic Market Information Tool,[69] the Personal Social Services Research Unit report on the unit costs of health and social care[72] and NHS reference costs[71] (see *Table 16*). All analyses assume that no costs of ART drugs are incurred in periods of interrupted treatment. Furthermore, potential ART drug waste from switching drug combinations before a package had been finished was not registered and therefore not estimated. All six categories of health-care resources consumed were included in the base-case analysis of costs accrued within 3 years. As such, the base case also includes the resource use that could mainly be attributed to the trial protocol (see *Table 16*).

Quality-adjusted life-years

The QALY is a generic measure of health that combines effects of interventions on both life expectancy and HRQoL and their side-effects and is defined as a year lived with full health.[66] To calculate the total QALYs gained per patient the length of life was weighted by the HRQoL. During the PIVOT trial, HRQoL was measured at baseline and at each scheduled follow-up visit using the three-level version of the European Quality of Life-5 Dimensions (EQ-5D-3L).[76] Responses were converted into the EQ-5D-3L index score using weights based on the UK value set.[77]

Missing data

Multiple imputation using chained equations was used to handle missing data on costs and outcomes.[78–80] The use of MI requires a less strong assumption regarding the missingness mechanism than the assumption needed to perform complete-case analysis. When complete-case analysis is performed in the presence of missing data it is assumed that there is no underlying relationship between missing values and any observed or unobserved variables; that is, that values are missing completely at random.[81] In contrast, MI requires that missing data can be assumed to be missing at random conditional on values of observed variables but not on any unobserved variables.[81] As such, missing data were handled using MI. A total of 20 imputations ($m = 20$) was performed as previous research suggested that $m = 20$ would improve efficiency in the presence of 10–30% missing data.[82] The model imputed HRQoL scores, ART drug costs, primary care costs, secondary care costs, the cost of HIV clinic visits and the cost of concomitant drug use at each 12-week time point. To further inform the imputation model the following auxiliary variables were included: age, gender, ethnic origin, baseline CD4 cell count, history of diabetes, smoking status, history of coronary artery disease, years of education, years since diagnosis, number of days off work between each time point and an indicator of whether patients were receiving a NNRTI-based or a PI-based regimen prior to randomisation. The imputation model performed predictive mean matching to handle the bounded and skewed nature of costs and HRQoL scores. In predictive mean matching the specified covariates are used to estimate a predictive model but, instead of replacing missing values with the model-predicted values, the nearest observed value is used to fill the missing value. By applying predictive mean matching, predictions that lie outside the bounds of each variable were avoided.[83] However, the distribution of imputed values will often closely match that of the observed values. Following the use of MI to generate estimates that replace missing values, the uncertainty of these values is incorporated in the estimation of mean costs and QALYs using a method commonly known as Rubin's rule.[84]

Regression analyses of costs and quality-adjusted life-years

Regression methods were used to obtain the incremental estimates of costs and QALYs between treatment groups while adjusting for the baseline characteristics that were selected a priori. A generalised linear model (GLM) was chosen as it offers a flexible framework to handle adjustment for baseline covariates when the distribution of the dependent variable is right skewed.[85] However, QALYs are usually left skewed.[86] Therefore, to be able to adjust the QALYs gained for baseline covariates, the QALY decrement was estimated. The QALY decrement is defined as the maximum QALYs that could possibly be accrued within the time frame minus the actual QALYs gained. Because the distribution of QALYs was left skewed, the distribution of QALY decrements was right skewed. Hence the GLM for right-skewed (gamma) distributions was a good match for both cost regressions and regressions of QALY decrements. An identity link function was applied to assume an additive effect of covariates on costs and QALY decrements.[85] Costs and QALY decrements were adjusted for the following baseline covariates: age, gender, ethnic origin, time since HIV diagnosis, history of diabetes, smoking status, history of coronary artery disease and CD4 cell count. In the regression of QALY decrements, the baseline HRQoL score was also included, as failure to do so may bias estimates in the presence of an imbalance in baseline HRQoL score between the treatment groups.[87] Regression analysis and MI of missing values was conducted in Stata version 12.1 (StataCorp, College Station, TX, USA).

Scenario analyses

Several scenario analyses were conducted to assess the impact of uncertainty on the cost-effectiveness results and to strengthen the external validity of the results; these are summarised in *Table 17*.

Scenarios 1a–f were constructed to incorporate potential reductions in the price of ARTs. Scenarios 1a–d assumed 10%, 20%, 30% and 40% reductions in the price of all ARTs respectively. Scenario 1e assumed a 10% reduction in the price of ART drugs in the PI-mono group and a 30% reduction in the price of ART drugs in the OT group. This scenario was constructed to explore the impact that generic versions of frequently used triple therapy drugs could be speculated to have on the cost-effectiveness of PI-mono compared with OT. Scenario 1f applied information about the current prices being paid, which was obtained through clinical advice with a HIV pharmacist in a major NHS trust.

TABLE 17 Alternative scenarios investigated

Scenario	Element	Base case	Variation for the sensitivity analysis
1	Costs	All unit costs for ART drugs were drawn from the Department of Health Commercial Medicines Unit's Electronic Market Information Tool[69] and the BNF[70]	1a: 10% reduction in all ART drug costs
			1b: 20% reduction in all ART drug costs
			1c: 30% reduction in all ART drug costs
			1d: 40% reduction in all ART drug costs
			1e: 30% reduction in ART drug costs for the OT group and 10% reduction in the PI-mono group
			1f: Estimated reductions obtained from personal communication with HIV pharmacist
2	Costs	All cost categories included	The costs that were deemed attributable to the trial protocol were excluded
3	Missing data	Data assumed to be missing at random; analysis therefore conducted on imputed data	Data assumed to be missing completely at random; analysis therefore conducted on the complete-case data
4	Mortality	All patients included	The six patients who died within 3 years were excluded from the analysis

In scenario 2 the costs of trial protocol-driven resource consumption were excluded as they might not be a part of routine clinical practice. PI monotherapy patients may need a stricter monitoring regimen than patients on triple therapy to ensure that combination therapy can be reintroduced promptly if a VL rebound occurs. The base case assumes that both PI-mono patients and OT patients attend scheduled HIV clinic visits every 12 weeks. Although this is considered reasonable in a routine clinical setting for PI monotherapy patients, it would be considered excessive for patients on triple therapy. Patients on triple therapy may only routinely attend scheduled HIV clinic visits every 24 weeks and the additional visits which the OT patients were subject to during the PIVOT trial were therefore considered to incur trial protocol-driven costs. This means that the trial protocol-driven consumption of health-care resources is higher in the OT group than in the PI-mono group. In scenario 2, these trial protocol-driven costs are excluded to assess the cost-effectiveness of PI monotherapy in a routine clinical setting. Hence scenario 2 assumes that PI-mono patients attend the HIV clinic every 12 weeks, whereas OT patients attend every 24 weeks. Furthermore, neurocognitive testing and PI drug concentration measurements conducted for the trial were excluded entirely.

In scenario 3 a complete-case analysis was performed to assess the impact of MI on the estimate of incremental costs and QALYs. GLM regression was also used in the complete-case analysis to adjust for baseline covariates. However, in the complete-case analysis QALY decrements could not be adjusted for history of diabetes and history of coronary artery disease because none of the complete cases was characterised by these at baseline. This was not considered to be a major issue as the restricted model for QALY decrements in the complete-case analysis was nested in the full model.

Scenario 4 addressed the within-trial mortality. The patients who died within 3 years (described in *Chapter 3*) were excluded from the analysis as it was considered unlikely that within-trial mortality was caused by treatment allocation. In total, six patients were removed from the data set after MI was performed. GLM regression of costs and QALY decrements was then performed using the remaining 291 PI-mono patients and 290 OT patients.

Subgroup analysis

In the PIVOT trial the randomisation of patients was stratified by whether ART treatment before randomisation was a PI-based or a NNRTI regimen. The stratification was carried out to ensure that equal numbers of patients from each stratum were randomised to each of the treatment groups because previous treatment was expected to impact on the success of the PI-mono strategy. This expected heterogeneity in treatment success is also likely to impact on costs and QALYs. Therefore, an exploratory subgroup analysis was conducted to investigate whether previous treatment regimen could be identified as a source of heterogeneity.[88] The subgroup analysis was performed by adding the previous regimen (PI based or NNRTI based) as a covariate and adding an interaction term between allocated treatment group (PI-mono or OT) and previous treatment regimen in regression models for costs and QALYs. As such, the subgroup analysis assumes that the impact of other covariates is independent of previous treatment.

Modelling lifetime costs and quality-adjusted life-years

The validity of the base case within the trial analysis for assessing cost-effectiveness relies on the assumption that no differences in costs or QALYs between the treatment groups persist beyond the trial follow-up period. As this can be considered a strong assumption, exploratory extrapolation was performed to assess the impact of differences persisting beyond the trial period. Two scenarios, A and B, were considered to model the future costs and QALYs by treatment group.

Scenario A assumed that PI-mono patients switch back to combination therapy 3 years post randomisation and that there is no difference in mortality between treatment groups; that is, the survival rates are equal in the trial and survival curves are assumed to be parallel following the end of the trial. Therefore, scenario A excluded from the analysis the patients who died within 3 years' follow-up, as in scenario 4 of the sensitivity analysis. Patient-specific life expectancies were calculated using a predictive model from the UK Collaborative HIV Cohort (UK CHIC) study[89] and data on mortality in the UK general population from the Office for National Statistics.[90] May *et al.*[89] have estimated life expectancy conditional on CD4 cell count and defined three groups: < 100, 100–199 and 200–350 cells/mm^3. The CD4 cell count measured at the closest point to the final 3-year follow-up visit was used to allocate the trial participants into these three groups to estimate patient-specific life expectancy conditional on age and CD4 cell count. The life expectancy of patients with a CD4 cell count of > 350 cells/mm^3 was estimated based on the group with a CD4 cell count of 200–350 cells/mm^3. Each patient's future HRQoL score was calculated from the HRQoL score at the final 3-year follow-up visit, with declining health over time being captured using an annual decrement per year of –0.00029.[91] QALYs were then calculated from the patient-specific life expectancy and HRQoL score. As this scenario assumes that PI-mono patients switch to OT at the end of the trial, the mean total cost per year in the OT group during the PIVOT trial was applied in both groups.

Scenario B assumed that all patients stay on the treatment that they were receiving at the end of the trial. As an extension of this assumption, it was assumed that any within-trial difference in mortality rate would continue beyond the trial follow-up period. In other words, a hazard ratio of 3.3 for all-cause mortality of PI-mono compared with OT was assumed to continue beyond the 3-year follow-up, allowing the survival curves to diverge at a constant rate. Life expectancy for OT patients was modelled in the same manner as in scenario A, whereas the hazard ratio for mortality within 3 years' follow-up was applied for patients in the PI-mono group to obtain life expectancy. However, the PI-mono patients who have switched back to triple therapy are assumed to have the same increased mortality rate as those still on PI monotherapy. To inform estimates of future costs, the within-trial costs between week 108 and week 156 were used. By the end of the 3-year follow-up period approximately 40% of PI-mono patients had switched back to triple therapy (see *Table 16*). By using the costs accrued during the final 48 weeks to inform future costs, the cost savings from PI monotherapy are diminished because many patients had switched back to triple therapy. At the patient level, costs accrued in the 48 weeks from week 108 to week 156 were inflated to reflect an entire year and applied as the annual cost of treatment until death. As such, scenario B was constructed to assess the cost-effectiveness of PI-mono under much less favourable assumptions for PI-mono; that is, a high mortality rate among PI-mono patients.

Probabilistic sensitivity analysis

The uncertainty surrounding the decision to adopt PI monotherapy was assessed using probabilistic sensitivity analysis (PSA) for every scenario. The PSA captures the uncertainty in all parameters jointly to estimate the probability of a treatment being cost-effective for a given cost-effectiveness threshold. The variance–covariance matrices from the regressions of costs and QALY decrements were extracted and entered in Microsoft Excel® 2010 (Microsoft Corporation, Redmond, WA, USA). The PSA was performed by taking 10,000 random draws from the distribution of the covariates in the regressions of costs and QALY decrements. The Cholesky decomposition was applied to ensure an appropriate covariance in the random draws. The 10,000 random draws were then used to present cost-effectiveness acceptability curves.[86] These were used to assess the probability of PI-mono being cost-effective across a range of cost-effectiveness thresholds.[92]

Results

Missing data

Missing data was not a major issue during the PIVOT trial. The EQ-5D-3L index score had the lowest number of available data, but none of the categories of HRQoL or resource use had > 20% missing values (*Table 18*).

TABLE 18 Percentages of available data on HRQoL and resource use

	EQ-5D-3L index score		ART drugs		HIV clinic visits		Primary care		Hospital Services		Trial protocol driven		Concomitant drugs	
Time point	PI-mono	OT	PI-mono	OT	PI-mono	OT	PI-mono	OT	PI-mono	OT	PI-mono	OT	PI-mono	OT
Baseline	97.6	98.3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
12 weeks	95.6	92.1	100.0	99.3	100.0	99.3	100.0	99.3	99.3	98.6	100.0	100.0	100.0	99.3
24 weeks	94.6	91.1	99.7	99.3	98.3	98.6	98.3	98.6	98.3	98.6	100.0	100.0	99.7	99.3
36 weeks	91.6	89.3	99.7	99.0	97.6	96.6	97.6	96.6	97.6	96.6	100.0	100.0	99.7	99.0
48 weeks	92.6	91.4	99.3	98.6	97.6	96.9	97.6	96.9	97.6	96.9	100.0	100.0	99.3	98.6
60 weeks	92.2	88.3	99.0	98.6	98.3	97.3	98.3	97.3	98.3	97.3	100.0	100.0	99.0	98.6
72 weeks	91.9	90.7	99.0	98.3	96.6	96.2	96.6	96.2	96.6	96.2	100.0	100.0	99.0	98.3
84 weeks	90.9	88.3	98.6	98.3	96.3	95.9	96.3	95.9	96.3	95.9	100.0	100.0	98.6	98.3
96 weeks	90.2	91.8	99.0	97.9	96.6	96.2	96.6	96.2	96.6	96.2	100.0	100.0	99.0	97.9
108 weeks	88.2	82.5	99.0	97.9	97.0	95.9	97.0	95.9	97.0	95.9	100.0	100.0	99.0	97.9
120 weeks	89.9	88.3	98.6	97.9	97.0	96.2	97.0	96.2	97.0	96.2	100.0	100.0	98.6	97.9
132 weeks	89.9	87.3	98.0	97.9	96.3	95.2	96.3	95.2	96.3	95.2	100.0	100.0	98.0	97.9
144 weeks	87.8	89.0	98.6	97.6	95.9	95.2	95.9	95.2	95.9	95.2	100.0	100.0	98.6	97.6
156 weeks	82.4	80.0	98.3	96.9	95.9	93.8	95.9	93.8	95.9	93.8	100.0	100.0	98.3	96.9

NA, not applicable.

Health-related quality of life

The missing values were handled using MI and the results are presented in *Table 19*. No marked difference in EQ-5D-3L index score was observed during the 156 weeks of follow-up in the PIVOT trial.

Costs

Missing values of costs were multiply imputed for each category at each time point. The degree of missing data for each of the six categories of health-care resources is shown in *Table 18*. The costs accrued within 3 years are shown by category in *Table 20*.

TABLE 19 Health-related quality of life (EQ-5D-3L index score) within the 3-year follow-up period

Time point	PI-mono ($n = 296$, $m = 20$), mean (SE)	OT ($n = 291$, $m = 20$), mean (SE)
Baseline	0.8772 (0.0102)	0.8716 (0.0111)
12 weeks	0.8512 (0.0130)	0.8481 (0.0135)
24 weeks	0.8601 (0.0137)	0.8672 (0.0128)
36 weeks	0.8585 (0.0134)	0.8617 (0.0129)
48 weeks	0.8369 (0.0145)	0.8328 (0.0146)
60 weeks	0.8398 (0.0144)	0.8389 (0.0150)
72 weeks	0.8433 (0.0143)	0.8418 (0.0153)
84 weeks	0.8497 (0.0140)	0.8564 (0.0135)
96 weeks	0.8209 (0.0156)	0.8312 (0.0141)
108 weeks	0.8418 (0.0134)	0.8479 (0.0144)
120 weeks	0.8317 (0.0155)	0.8553 (0.0131)
132 weeks	0.8226 (0.0161)	0.8544 (0.0138)
144 weeks	0.8194 (0.0153)	0.8343 (0.0146)
156 weeks	0.8145 (0.0164)	0.8326 (0.0156)

Multiple imputation ($m = 20$) using chained equations was used to handle missing values of HRQoL at every time point.

TABLE 20 Unadjusted costs accrued within 3 years by category

	PI-mono ($n = 296$, $m = 20$)		OT ($n = 291$, $m = 20$)	
Cost category	Mean (SE) (£)	% of total	Mean (SE) (£)	% of total
ART drugs	14,335.31 (286.52)	62.5	21,954.84 (255.39)	74.9
HIV clinic visits	6648.38 (100.08)	29.0	3359.13 (112.04)	11.5
Primary care	325.52 (19.15)	1.4	316.26 (21.24)	1.1
Hospital services	1010.49 (120.40)	4.4	988.46 (126.55)	3.4
Trial protocol driven	574.32 (6.82)	2.5	2676.92 (25.67)	9.1
Concomitant drugs	30.71 (6.70)	0.1	27.84 (7.40)	0.1
Total	22,924.74 (354.42)	100	29,323.46 (337.72)	100

Multiple imputation ($m = 20$) using chained equations was used to handle missing values in each category of costs at every time point. Cost accrued beyond the first year is discounted at an annual rate of 3.5%.

From *Table 20* it can be seen that the unadjusted incremental cost of PI-mono was –£6398.72 per patient within 3 years. The single largest difference between the groups is in the cost of ART drugs. Considerably more costs were incurred from HIV clinic visits in the PI-mono group. This is because the scheduled HIV clinic visits every 12 weeks were considered to be necessary for the PI-mono strategy outside the trial setting, whereas scheduled visits only every 24 weeks were considered necessary in the OT group. Conservatively, even those patients who switched from PI monotherapy back to combination therapy were considered to have scheduled visits every 12 weeks. As patients in both trial arms were seen every 12 weeks for scheduled HIV clinic visits, the additional visits in the OT group were considered to be trial protocol-driven costs. As such, the trial protocol-driven costs are considerably higher for the OT group than for the PI-mono group. Costs incurred from primary care, hospital services and cholesterol-lowering treatments were comparable between groups within 3 years.

Cost-effectiveness

Base-case analysis

In the base-case analysis PI-mono was a dominant strategy as it offered, per patient, both mean cost savings and a small mean QALY gain compared with OT. The adjusted incremental total cost of PI-mono per patient was –£6424.11 (95% CI –£7418.84 to –£5429.38) over a 3-year period. The cost savings in the PI-mono group were mainly attributable to the saving in ART drug costs. The adjusted regression of QALY decrements showed that PI-mono patients gained an average of 0.0051 QALYs (95% CI –0.0479 to 0.0582) more than OT patients (*Table 21*). The PSA revealed that PI-mono was cost-effective in 100% of simulations regardless of whether a £20,000 per QALY or a £30,000 per QALY cost-effectiveness threshold was applied (*Figure 14*).

Scenario analyses

Overall, PI-mono remained cost-effective in all scenarios. The results were robust regarding all of the alternative ART prices used in scenario 1. However, scenario 1e showed that introduction of generic versions of frequently used triple-therapy drugs resulted in a 20% larger reduction in the mean ART cost for OT and much lower cost savings for PI-mono. Scenario 2, in which PI-mono requires a stricter monitoring regimen than OT in routine clinical practice but in which other trial protocol-driven costs were excluded, resulted in a mean cost saving of £4307.27 per patient for PI-mono. In the complete-case analysis performed for scenario 3, differential costs and QALYs fell in the south-west quadrant of the cost-effectiveness scatterplot; that is, PI-mono remained cost-saving but resulted in a QALY decrement compared with OT. However, the PSA showed that PI-mono remained cost-effective as the mean QALY loss was small (–0.0227, 95% CI –0.0878 to 0.0424) but there were large cost savings. Under the assumption that the observed within-trial mortality was unrelated to the allocated treatment, the six patients who died were excluded from the analysis in scenario 4. The expected QALY gain observed in the PI-mono group was slightly higher than in the base-case analysis as five out of the six patients who died within 3 years' follow-up were allocated to the PI-mono group. The results of all alternative scenarios are summarised in *Table 21*.

Subgroup analysis

The results of the exploratory subgroup analysis demonstrated that PI-mono was cost-effective in both strata. Results indicated that patients who were receiving a PI-based regimen before randomisation had larger mean cost savings from PI-mono than those receiving a NNRTI-based regimen. Furthermore, PI-mono might be associated with a slight QALY loss for patients receiving a NNRTI-based regimen. For both strata, PI-mono was considered cost-effective in 100% of the simulations regardless of whether a £20,000 per QALY or a £30,000 per QALY threshold was applied (*Figure 15*).

TABLE 21 Cost-effectiveness results of all scenarios

Analysis	Incremental cost (PI-mono – OT) (95% CI) (£)	Incremental QALYs (PI-mono – OT) (95% CI)	ICER (£)	Probability of being cost-effective at threshold of £20,000 per QALY (£30,000 per QALY) (%)
Base-case analysis				
Base case	–6424.11[a] (–7418.84 to –5429.38)	0.0051[a] (–0.0479 to 0.0582)	PI-mono dominant	100 (100)
Alternative scenarios[b]				
Scenario 1a	–5662.98[a] (–6589.23 to –4736.73)	0.0051[a] (–0.0479 to 0.0582)	PI-mono dominant	100 (100)
Scenario 1b	–4902.03[a] (–5762.35 to –4041.71)	0.0051[a] (–0.0479 to 0.0582)	PI-mono dominant	100 (100)
Scenario 1c	–4141.32[a] (–4938.84 to –3343.79)	0.0051[a] (–0.0479 to 0.0582)	PI-mono dominant	100 (100)
Scenario 1d	–3380.89[a] (–4119.48 to –2642.29)	0.0051[a] (–0.0479 to 0.0582)	PI-mono dominant	100 (100)
Scenario 1e	–1279.97[a] (–2134.85 to –425.08)	0.0051[a] (–0.0479 to 0.0582)	PI-mono dominant	97.47 (93.84)
Scenario 1f	–4245.63[a] (–5085.79 to –3405.47)	0.0051[a] (–0.0479 to 0.0582)	PI-mono dominant	100 (100)
Scenario 2	–4307.27[a] (–5285.24 to –3329.31)	0.0051[a] (–0.0479 to 0.0582)	PI-mono dominant	100 (100)
Scenario 3	–6417.15[c] (–7393.62 to –5440.68)	–0.0227[d] (–0.0878 to 0.0424)	282,641[e]	100 (100)
Scenario 4	–6406.41[f] (–7374.08 to –5438.74)	0.0197[f] (–0.0291 to 0.0685)	PI-mono dominant	100 (100)
Subgroup analysis				
PI-based regimen at randomisation	–9718.45[a] (–11,183.1 to –8253.8)	–0.0032[a] (–0.0804 to 0.0741)	3,085,027[e]	100 (100)
NNRTI-based regimen at randomisation	–7386.40[a] (–8910.89 to –5861.90)	–0.0316[a] (–0.1094 to 0.0462)	233,639[e]	100 (100)
Modelling of lifetime cost-effectiveness				
Scenario A	–38,248[f] (–46,081 to –30,416)	–0.3884[f] (–1.1299 to 0.3531)	98,475[e]	99.98 (98.52)
Scenario B	–69,065[f] (–76,212 to –61,919)	–3.2597[f] (–3.8945 to –2.6249)	20,772[e]	63.31 (0.19)

a PI-mono ($n = 296$, $m = 20$) and OT ($n = 291$, $m = 20$).
b The details of the alternative scenarios are provided in *Table 17*.
c PI-mono ($n = 266$, $m = 0$) and OT ($n = 254$, $m = 0$).
d PI-mono ($n = 142$, $m = 0$) and OT ($n = 130$, $m = 0$).
e ICER in the south-west quadrant of the cost-effectiveness plane, i.e. the ICER of OT compared with PI-mono.
f PI-mono ($n = 291$, $m = 20$) and OT ($n = 290$, $m = 20$).

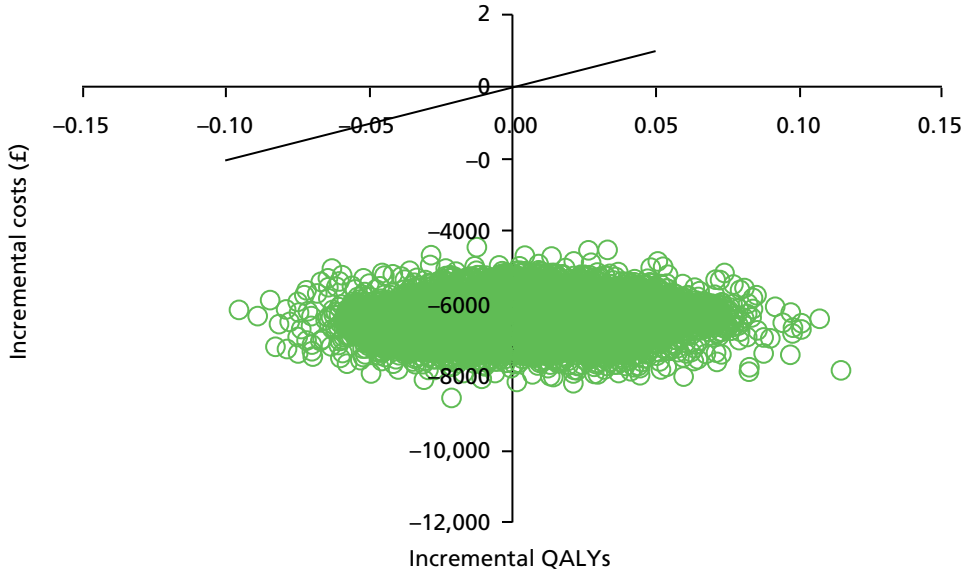

FIGURE 14 Incremental cost-effectiveness scatterplot for the base-case analysis (PI-mono – OT). The green circles are the 10,000 simulated sets of the incremental costs and QALYs of PI-mono compared with OT in the PSA for the base-case analysis. The black line running through (0,0) in the cost-effectiveness plane is the £20,000 per QALY threshold. As all simulations fall 'under' the threshold PI-mono could be considered cost-effective compared with OT in 100% of the simulations.

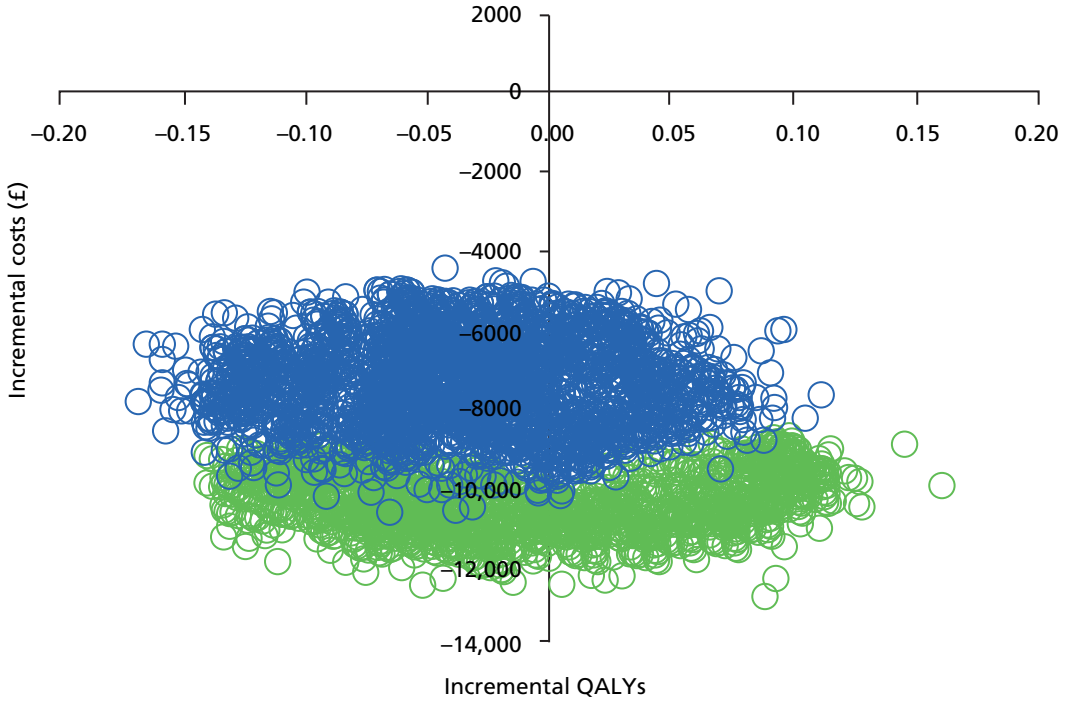

FIGURE 15 Incremental cost-effectiveness scatterplot for the subgroup analysis (PI-mono – OT). The blue circles are the 10,000 simulated sets of incremental costs and QALYs of PI-mono compared with OT for patients receiving a NNRTI-based regimen at randomisation, whereas the green circles are the 10,000 simulated sets of incremental costs and QALYs for patients receiving a PI-based regimen at randomisation.

Extrapolation

In both of the exploratory extrapolation scenarios PI-mono was cost saving but also less effective than OT. However, the substantial cost saving associated with PI-mono in both scenarios means that PI-mono may be cost-effective. This is because the costs saved by the use of PI-mono could generate more QALYs if spent elsewhere than the small amount of QALYs lost to the patients on PI-mono. As PI-mono is cost saving and less effective, the results fall in the south-west quadrant of the cost-effectiveness plane (*Figure 16*).

In this quadrant, the ICER can be interpreted as the difference in costs between the lower-cost intervention (PI-mono) and the higher-cost intervention (OT), such that each additional QALY offered by OT over PI-mono costs the ICER value. Consequently, the ICERs of £98,475 per QALY and £20,772 per QALY in scenarios A and B, respectively, represent the ICERs of OT compared with PI-mono (i.e. the incremental cost of OT compared with PI-mono per additional QALY generated by OT compared with PI-mono). Therefore, at a cost-effectiveness threshold of £20,000 per QALY, PI-mono appears to be the cost-effective option in both extrapolation scenarios, as the incremental cost per QALY generated by OT compared with PI-mono is above the threshold in both cases. At a threshold of £30,000 per QALY, OT appears to be cost-effective in scenario B, generating additional QALYs at a cost below the threshold, but not in scenario A. There are two main reasons for the difference in the results of the two extrapolation scenarios. First, the lower effectiveness of PI-mono in extrapolation scenario B is caused by the assumption that the PI-mono group has a hazard ratio of 3.3 for all-cause mortality compared with the OT group. Second, the higher cost saving in extrapolation scenario B is caused by the assumption that the majority of patients in the PI-mono group continue lifelong monotherapy.

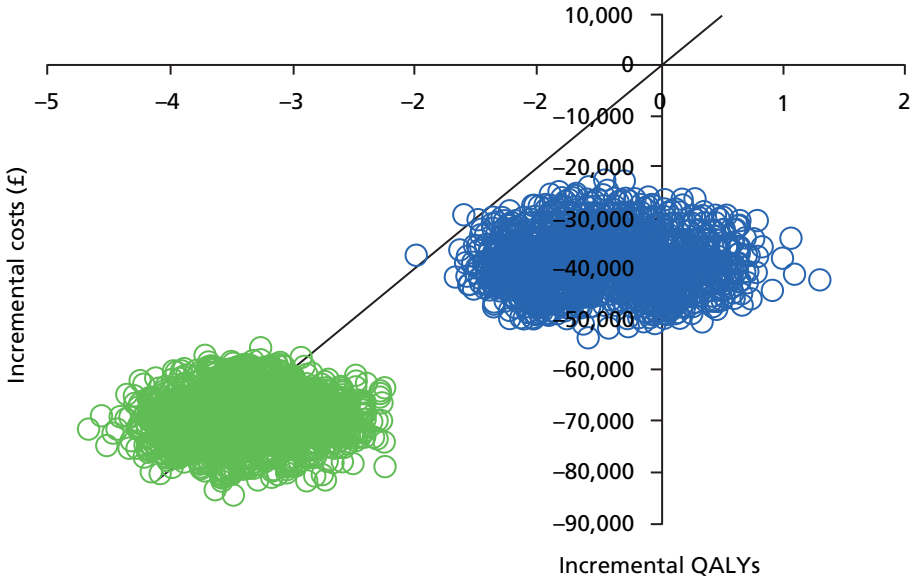

FIGURE 16 Incremental cost-effectiveness scatterplot for the two extrapolation scenarios (PI-mono – OT). The blue circles are the 10,000 simulated sets of incremental costs and QALYs of PI-mono compared with OT for extrapolation scenario A, whereas the green circles are the 10,000 simulated sets of incremental costs and QALYs for extrapolation scenario B. The black line running through (0,0) in the cost-effectiveness plane is the £20,000 per QALY threshold.

Chapter 5 Discussion

Main trial results

We have shown that, in patients who have achieved VL suppression on combination therapy, a maintenance strategy of PI monotherapy with reintroduction of combination therapy in the event of VL rebound was non-inferior to combination therapy in preserving future treatment options over 3–5 years. Only one patient developed clinically significant resistance to the PI that they were taking as monotherapy, an I50L mutation occurring on atazanavir monotherapy. The clinical consequences of this are mitigated by the increase in sensitivity to other PIs conferred by this mutation.[93] None of the 278 patients taking DRV or LPV (the recommended options for monotherapy, taken by the large majority of the patients in this trial) developed resistance affecting the efficacy of these drugs. Our findings concur with earlier trials of PI monotherapy that found little resistance but extend these results to provide the critical long-term randomised outcome data in a large pragmatic trial needed to provide the confidence to use this option in clinical practice.[17,24,25,46] We sought resistance fastidiously, testing confirmed VL rebound samples irrespective of level of viraemia, using standard population sequence genotypic testing. Although PI resistance may occur in other regions of the virus, such as in the *gag* or *env* genes, or in minority species that are not detected by population assays,[12] previous minority species sequencing in patients failing PI monotherapy has found minimal resistance in excess of that detected by population sequencing.[36,37,94] Furthermore, our finding that patients with VL rebound on PI monotherapy achieved full VL suppression without exception when switched to combination therapy (usually by reintroduction of NRTIs) provides an important assurance that any mutations that were not detected by population sequencing did not impact on subsequent treatment efficacy.

A higher proportion of patients in the PI-mono group experienced VL rebound. This had been expected, although the difference was much greater than that seen in previous studies.[31] VL suppression has been the traditional outcome for comparing treatment regimens in clinical trials but is less informative in strategy trials such as this, especially given the different impact of VL rebound on risk of drug resistance for different drug classes. Aside from risk of resistance (shown to be minimal in this study), it is unlikely that these brief episodes of low-level viraemia, rapidly reversed by the reintroduction of combination therapy, would have adverse long-term effects – persistent VL levels of > 20,000 copies/ml are needed to drive HIV disease progression.[95] Indeed, there was no evidence of excess HIV disease progression in the PI-mono group, as increases in CD4 cell counts and HIV disease-related clinical events were similar between the two groups. Although deaths were numerically greater in the PI-mono group this was not statistically significant as the causes were diverse and without plausible link to the drugs taken or HIV disease progression. We therefore regard this as a chance imbalance, but will continue to follow the trial cohort to gather further outcome data.

Fewer episodes of renal impairment were seen in the PI-mono group, as anticipated given the well-recognised renal toxicity of NRTIs (especially tenofovir). However, close laboratory monitoring and pre-emptive treatment changes ensure that serious renal outcomes are rare; there were no cases of end-stage renal disease in the standard-of-care group.[96] This pragmatic trial, in which clinicians were allowed to switch drugs at clinical discretion (rather than be restricted to single protocol-mandated regimens), provides a realistic estimate of the clinical impact of PI monotherapy in routine clinical practice and suggests that the benefits in terms of renal toxicity would be modest. We did not find any other clinical advantages of the PI monotherapy strategy. A potential theoretical concern expressed about PI monotherapy has been that suboptimal drug penetration into the CNS might lead to harm.[20,44] Neurocognitive testing carried out in all patients throughout the trial found no differences between the groups. This, together with the absence of a significant excess of neurological events in the PI-mono group, provides important reassurance that even if PI monotherapy has less brain penetration this does not lead to important clinical consequences.

The strengths of this trial are its size and duration (more than three times the randomised person follow-up time of earlier studies), the low loss to follow-up rate, the pragmatic design set in routine clinical care with flexibility in drug selection in both treatment groups and the use of a primary efficacy end point (preserving drug options) that is relevant to long-term management. Limitations are the open-label design and the lack of pre-ART resistance tests in some patients, which would help to rule out resistance acquired before the trial (both limitations were unavoidable). Although the primary end point and many of the major secondary end points were based on measured laboratory values, the possibility of bias needs to be considered in some of the secondary end points that incorporated subjective measures as part of the assessment, in particular clinical AEs, neurocognitive assessment and quality of life assessment.

Bias in the reporting of clinical AEs could arise from selective reporting of events by patients or selective ascertainment by clinicians or study staff (e.g. by prompting specifically about symptoms that the researchers believe, correctly or incorrectly, to be associated with particular treatment arms, such as neurocognitive events in the PI-mono arm and peripheral neuropathy events in the standard-of-care arm); selective recording of events or systematic differences in grading of those events in the medical record; or selective reporting of events captured in the medical record in the case report form (and hence entry into the trial database). To minimise the risk of bias we compared treatment arms using events at the more severe end of the spectrum only (i.e. grades 3 and 4), which are less likely to go unreported by patients or unrecorded in the medical case notes. Sites were provided with standard tables for grading events, were trained on the use of these and were required to report all grade 3 or 4 events (or serious disease progression events or SAEs) on a separate event form together with justification for choosing the grade. These forms were checked independently by a clinician at the trial co-ordinating centre and any apparent misclassification was discussed with the site. Finally, on-site monitoring was carried out at all sites, with a random selection of the medical records reviewed to detect any events that had not been reported on the case report forms (with more detailed inspection if any discrepancies were detected). We believe that these measures reduced any bias in the collection of clinical AEs to a minimum, although we cannot rule it out completely. There was a trend (although not significant) towards a greater number of reported CNS grade 3 or 4 events in the PI-mono arm, but the heterogeneous nature of these events argues against a common aetiology; this is most likely a chance imbalance or possibly minor residual bias towards reporting such events in the PI-mono arm. The method of conducting neurocognitive tests was standardised and the sites were trained to follow these methods uniformly for all patients, therefore it would be difficult for bias to be introduced by staff members performing the testing. In general, patients were self-motivated to give their best performance on the tests and it is unlikely that any of them deliberately modulated their performance in response to some belief about their treatment allocation. Both treatment groups improved performance over time (as might be expected with a learning effect), with similar changes in both groups, again suggesting that bias is unlikely. The assessment of quality of life used a well-validated questionnaire that the patients self-completed and so this could not be influenced by site staff. It is the patients' perception of their condition that matters in the assessment of quality of life, and it is academic whether that is determined by subjective opinion about the impact of the treatment that they are taking or the direct effects caused by treatment benefits or side effects.

We believe that the pragmatic trial design, broad inclusion criteria and other strengths of the trial outlined above mean that the results are likely to be generalisable to other settings internationally where treatment is individualised and regular VL monitoring is performed. We excluded patients with active substance abuse or psychiatric illness if this was considered severe enough to preclude compliance with the trial protocol. In some clinic settings, a high proportion of patients have psychiatric comorbidity. Although our trial findings do not strictly apply to this group, such patients might be expected to do better on PI monotherapy given what is known (including from this trial) about PI resistance being slow to develop in patients with episodes of VL rebound. In fact, the European HIV treatment guidelines[32] (see *Conclusions*) recommend these patients as a particular group to consider for PI monotherapy. We also excluded patients with high CVD risk at baseline because of concerns that being randomised to start a PI might increase that risk. The current British HIV Association (BHIVA) treatment guidelines[97] recommend avoiding LPV in such patients but offer no opinion on the use of DRV, the other main drug used for PI monotherapy, so this may still represent a feasible group for treating with PI monotherapy.

Cost-effectiveness

The results showed that switching to a strategy of PI-mono, with prompt return to combination therapy in the event of VL rebound, was cost-effective compared with OT in most scenarios. Within 3 years there was little difference in the mean QALYs between PI-mono and OT. PI-mono appears to be cost-effective compared with OT as substantial resources could be freed from HIV treatment and used to improve health outcomes for other patients. In the sensitivity analyses and extrapolation scenarios, PI-mono was cost saving but marginally less effective than OT. In all but extrapolation scenario B at a threshold of £30,000 per QALY, PI-mono appeared to be cost-effective compared with OT. This was because the cost saving from PI-mono could generate more health elsewhere than the small amount of health lost to PI-mono patients.

Two studies have investigated ART drug costs following PI-based monotherapy compared with the ART drug costs of triple therapy.[98,99] In both studies the estimated ART drug cost in the PI monotherapy group was comparable to that in the present study. However, in both studies the estimated cost of ART drugs in the combination therapy group was higher than that in the present study. The study by Restilli *et al.*[99] also investigated the total health-care costs of PI monotherapy patients and compared them to the total health-care costs of patients on combination therapy using Italian administrative records. It was estimated that the incremental cost of PI monotherapy compared with combination therapy would be –€3382 per year. This represents an approximate cost saving of £8000 over a 3-year period, compared with the present base-case analysis in which the cost saving was estimated to be £6424 per patient over a 3-year period. A noticeable similarity between the present study and the study by Restilli *et al.*[92] is that the base-case analyses in both studies assumed that both treatment groups would attend the same number of outpatient activities. However, this might not be the case in routine clinical practice. The present study therefore conducted sensitivity analyses (scenario 2) to assess the cost-effectiveness of monotherapy in a situation in which PI-mono patients are routinely followed every 12 weeks and OT patients are followed every 24 weeks. In this scenario the cost saving of PI-mono was reduced to £4307 over a 3-year period. In the health technology assessment by Restilli *et al.*[99] it was concluded that the evidence supported the use of PI-based monotherapy as an alternative to combination therapy. In the study by Gazzard *et al.*[98] the ART drug costs of DRV/ritonavir-based monotherapy were compared with those of combination therapy from a UK perspective. They used trial data on ART drug consumption from the MONET trial[22] and did not consider total health-care expenditure. Gazzard *et al.*[98] estimated an annual cost saving for ART drugs of £4126 (that is £12,378 over 3 years), whereas the present study estimated the 3-year cost saving to be £7620. However, Gazzard *et al.*[98] also acknowledge that, although patients on combination therapy may need scheduled visits to HIV clinics only every 6 months, patients on PI monotherapy may need to be seen every 3 months, which would reduce their estimated cost saving.

The strengths of this economic evaluation are that it presents the costs and QALYs accrued in a large randomised trial designed to reflect routine clinical practice as closely as possible. As such, the results are highly relevant to decision-makers.

A few limitations of the cost-effectiveness analysis should be noted. First, a within-trial cost-effectiveness analysis is limited by the assumption that costs and outcomes do not differ between treatment groups after the follow-up period. This is a significant assumption that might not hold in the context of managing HIV-1-infected patients. Two extrapolation scenarios were generated to address this limitation. The results showed that PI-mono could be considered cost-effective in both extrapolation scenarios at a £20,000 per QALY threshold. However, for a cost-effectiveness threshold of £30,000 per QALY, OT would be considered the more cost-effective form of management.

Second, the May *et al.*[89] data used for modelling life expectancies in extrapolation scenarios A and B are subject to uncertainties. Notably, the data used to estimate life expectancies are extrapolated well beyond what is observed and there is still a lack of data in the older age group where most of the mortality is in the general population.

Third, the analysis is limited by the manner in which data on health-care resource consumption were collected. During the PIVOT trial, patients were asked to recall their contacts with the health-care system since the last follow-up visit. Although there might not be an issue with data validity for patients who attended each 12-week visit, the risk of recollection bias is likely to increase if one or more visits are missed. However, any such recollection bias is thought to have restricted influence on the estimates of the incremental costs. The costs of primary care, hospital services and concomitant drugs accounted for only 5–6% of the total cost and therefore any imprecision in the costs of these would have a diminished importance in terms of the incremental cost.

Fourth, the cost-effectiveness results presented in this study are conditional on the current ART prices. Scenarios 1a–f attempted to explore the impact that variation in ART drug prices could have on the cost-effectiveness results. However, there is uncertainty surrounding future ART prices and these analyses should be viewed as speculative. The ART treatment regimens taken by patients in the OT arm of the trial were typical of the standard-of-care regimens in use at the time that the study started and of those that continue to be used at the time of writing this report. However, a new class of drugs, integrase inhibitors, have been developed that in some cases appear to have clear advantages over the current drugs in terms of toxicity and possibly efficacy.[100] These are now licensed for the initial treatment of HIV infection in the UK. Although cost has limited their uptake to date, as prices fall it is likely that they will become more widely used over the next 5–10 years, possibly becoming the dominant drugs used in treating HIV infection. They are still required to be given in combination therapy, usually with NRTIs. The cost-effectiveness calculations may therefore change with the shift in clinical practice in HIV therapy.

Conclusions

Although there have been a number of trials of PI monotherapy conducted previously, the majority of which have been initiated and funded by the pharmaceutical industry, this large, long-term, strategic, investigator-initiated and publicly funded trial is likely to be regarded as the definitive trial of PI monotherapy because it has answered the clinically relevant long-term impact questions that previous trials were unable to address convincingly. There are no ongoing RCTs of PI monotherapy of greater size or duration than the PIVOT trial and it is unlikely now that any will be undertaken in the future. Additional meta-analyses may be performed that will incorporate the PIVOT trial data to assess VL suppression rates (which we have shown to be of limited value as an end point), but this is unlikely to affect the broad conclusion drawn from this trial, which is that there is a higher rate of VL rebound with PI monotherapy but that this does not adversely impact on future treatment options.

The PIVOT trial identified a numerical excess of deaths (not statistically significant) in the PI-mono arm that were of diverse aetiology and considered to be unrelated to the treatment strategy and are most likely to be a chance finding. Consent was obtained at the last patient visit to continue follow-up of the cohort (both treatment groups) for a further 5 years. This will be carried out by means of annual retrospective data collection from patient clinical case sheets/records gathered at routine clinical visits, collecting outcome data on VL rebound episodes, drug resistance, treatment changes and major clinical events. It is likely that a substantial proportion of patients who have been stable on PI monotherapy will choose to remain on this strategy and so the follow-up will provide additional valuable data on longer-term outcomes. This additional follow-up, with likely accumulation of more clinical events, may be of particular value in addressing any residual concerns around the imbalance in the (small) number of deaths, as well as other outcome differences between the groups that may become more pronounced with longer-term follow-up (e.g. renal function).

The impact of the PIVOT findings on HIV treatment guidelines is hard to predict at this point. Current BHIVA treatment guidelines (2014 update, unchanged from the 2012 version)[97] recommend 'continuing standard combination ART as the maintenance strategy in virologically suppressed patients. There are insufficient data to recommend PI/r monotherapy in this clinical situation.' Current European AIDS Clinical Society (EACS) treatment guidelines (2014 edition)[32] recommend that 'PI/r monotherapy with qd DRV/r or

bd LPV/r might represent an option in persons with intolerance to NRTIs or for treatment simplification or in illicit drug users with documented frequent interruption of cART. Such a strategy only applies to persons without history of failure on prior PI-based therapy and who have had HIV-VL < 50 copies/ml in at least the past 6 months and who do not have chronic HBV.' The PIVOT findings would support recommending the PI-mono strategy more broadly as an acceptable treatment option for patients, but it is unclear whether this will in fact translate into guideline changes. The belief by physicians that VL rebound is a universally bad thing is deeply ingrained. Although it is clear from the PIVOT trial and other trials that PIs are very robust drugs that have a very low propensity to develop resistance after short-term low-level VL rebound, this nuanced thinking about the consequences of VL rebound may not gain traction given the longstanding mantra about the essentiality of triple therapy to prevent VL rebound. Furthermore, guideline panels use VL suppression and rebound rates as the unifying factor for decisions around regimens across trials of different designs and may be uncomfortable using alternative approaches to evaluate regimen strategies. Clear evidence of toxicity reduction with the PI-mono strategy could have represented a compelling argument for its adoption by guideline panels, but in the absence of this the risk–benefit assessment is more neutral. Nevertheless, the PIVOT trial has provided evidence that will increase the confidence of physicians to use this intervention in patients who are intolerant of NRTIs. Because such patients might have been randomised to the standard-of-care arm and be required to continue these NRTIs, such patients were excluded from entering this trial. Particular treatment groups, such as those with renal impairment on tenofovir, could benefit from PI monotherapy, although there may be alternatives to tenofovir use in this situation such as the NRTI abacavir or substituting an alternative drug class such as integrase inhibitors. Patients with challenges to adherence such as those with psychiatric illness may also do better on PI monotherapy because of the more limited risk of resistance developing with intermittent treatment, although that is different from the strategy we used here, which required immediate reintroduction for treatment failure. Switching to PI monotherapy is likely to be more attractive as an option when patients are already established on a PI-based triple therapy regimen as, in this case, the intervention involves simply withdrawing drugs, with the benefit of reducing pill burden and with no risk of new drug toxicity. For patients established on a NNRTI-based regimen, especially those taking a single combination pill once a day, switching to monotherapy may increase the pill burden slightly and also runs the risk of introducing new side effects arising from changing to a new drug class (PIs).

Although the findings of the PIVOT trial are unlikely to lead to a recommendation in clinical practice guidelines that PI monotherapy is the preferred approach, there may be other drivers of the increased use of this intervention. Anecdotally, many UK physicians report that they have substantial numbers of patients on PI monotherapy in their clinical practice and the PIVOT trial findings are likely to reassure them and increase their confidence that this is a perfectly reasonable approach. Furthermore, although clinical considerations are paramount in drafting treatment guidelines, when there are no compelling clinical advantages of using one ART regimen over another the relative costs often have a substantial impact on pragmatic decisions over which regimens are used in clinical practice. Given that under most of the scenarios evaluated switching to a strategy of PI-mono was shown to be cost-effective compared with OT for HIV-1-infected patients, this may increase the willingness to consider this intervention in practice. However, the financial drivers are likely to be dynamic given that a number of first-line ART drugs are coming off patent and there are increasing options for first-line therapy with the introduction of new classes of drugs such as integrase inhibitors, which are driving down drug costs. PIs are relatively expensive drugs to produce and it may be that combination therapy using generic drugs from other classes eventually becomes cheaper than PI monotherapy, thus removing this potential driver of the use of this therapy. Future combination drug prices are a key uncertainty in the cost-effectiveness analysis and if future prices are low it may alter the cost-effectiveness results.

The PIVOT trial has shown that PI monotherapy is an acceptable alternative to standard combination ART for long-term HIV management, with a modest benefit in terms of reducing renal toxicity. The need for regular VL monitoring and the possible requirement to switch back to combination therapy may be perceived as drawbacks, but this approach may nevertheless appeal to patients wishing to minimise drug exposure. More broadly, the trial challenges the mantra that combination therapy is essential for the management of chronic HIV infection.

Acknowledgements

Members of the PIVOT trial team

Participating UK sites

Elton John Centre, Brighton: Martin Fisher, Amanda Clarke, Wendy Hadley and David Stacey; Royal Free Hospital, London: Margaret Johnson and Pat Byrne; Mortimer Market Centre, London: Ian Williams, Nahum De Esteban, Pierre Pellegrino, Lewis Haddow and Alejandro Arenas-Pinto; Barts & the London Hospital, London: Chloe Orkin, James Hand, Carl De Souza, Lisa Murthen and Andrew Crawford-Jones; Royal Berkshire Hospital, Reading: Fabian Chen, Ruth Wilson, Elizabeth Green and John Masterson; Manchester Royal Infirmary: Vincent Lee, Kamlesh Patel and Rebecca Howe; St Mary's Hospital, London: Alan Winston and Scott Mullaney; Southmead Hospital, Bristol: Mark Gompels and Louise Jennings; Royal Liverpool University Hospital, Liverpool: Nicholas Beeching and Rebecca Tamaklo; Guy's and St Thomas' Hospital, London: Julie Fox, Alistair Teague, Isabelle Jendrulek and Juan Manuel Tiraboschi; North Manchester General Hospital, Manchester: Ed Wilkins, Yvonne Clowes and Andrew Thompson; Central Middlesex Hospital, London: Gary Brook and Manoj Trivedi; Avenue House Clinic, Eastbourne: Kazeem Aderogba and Martin Jones; Gloucester Royal Hospital: Andrew DeBurgh-Thomas and Liz Jones; Homerton University Hospital, London: Iain Reeves and Sifiso Mguni; James Cook University Hospital, Middlesbrough: David Chadwick, Pauline Spence and Nellie Nkhoma; Derriford Hospital, Plymouth: Zoe Warwick, Suzanne Price and Sally Read; Royal Bournemouth Hospital, Bournemouth: Elbushra Herieka, James Walker and Ruth Woodward; Southend University Hospital, Westcliff-on-Sea: John Day and Laura Hilton; St Mary's Hospital, Portsmouth: Veerakathy Harinda and Helen Blackman; St George's Hospital, London: Phillip Hay, Wendy Mejewska and Olanike Okolo; Royal Victoria Infirmary, Newcastle: Edmund Ong, Karen Martin and Lee Munro; Royal Hallamshire Hospital, Sheffield: David Dockrell and Lynne Smart; North Middlesex University Hospital, London: Jonathan Ainsworth and Anele Waters; Queen Elizabeth Hospital, Woolwich: Stephen Kegg and Sara McNamara; Birmingham Heartlands Hospital, Birmingham: Steve Taylor and Gerry Gilleran; Chelsea & Westminster Hospital, London: Brian Gazzard and Jane Rowlands; University Hospital of Coventry: Sris Allan and Rumun Sandhu; Ealing Hospital, London: Nigel O'Farrell and Sheena Quaid; Harrogate District Hospital, Harrogate: Fabiola Martin and Caroline Bennett; Northwick Park Hospital, London: Moses Kapembwa; St James' Hospital, Leeds: Jane Minton and James Calderwood; King's College Hospital, London: Frank Post, Lucy Campbell and Emily Wandolo; Leicester Royal Infirmary, Leicester: Adrian Palfreeman and Linda Mashonganyika; Luton & Dunstable University Hospital, Luton: Thambiah Balachandran and Memory Kakowa; Newham University Hospital, London: Rebecca O'Connell and Cheryl Tanawa; Edith Cavell Hospital, Peterborough: Sinna Jebakumar and Lesley Hagger; Royal Victoria Hospital, Belfast: Say Quah and Sinead McKernan; York Teaching Hospital, York: Charles Lacey, Sarah Douglas, Sarah Russell-Sharpe and Christine Brewer; Western General Hospital, Edinburgh: Clifford Leen and Sheila Morris; Barking Hospital, London: Sharmin Obeyesekera and Shirley Williams; Norfolk and Norwich University Hospital, Norwich: Nelson David; Worcester Royal Hospital, Worcester: Mark Roberts and Julie Wollaston.

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Contributions of authors

All of the authors made substantial contributions to the conception and design of the trial or the acquisition, analysis and interpretation of data, all were involved in the drafting of the manuscript or revising it critically for important intellectual content and all approved the final version to be published.

Nicholas I Paton was involved in the design, conduct, analysis and reporting phases.

Wolfgang Stöhr was involved in the design, conduct, analysis and reporting phases.

Lars Oddershede was involved in the analysis and reporting phases.

Alejandro Arenas-Pinto was involved in the design, conduct, analysis and reporting phases.

Simon Walker was involved in the analysis and reporting phases.

Mark Sculpher was involved in the design, analysis and reporting phases.

David T Dunn was involved in the design, conduct, analysis and reporting phases.

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Winston A, Arenas-Pinto A, Stöhr W, Fisher M, Orkin CM, Aderogba K, *et al.* Neurocognitive function in HIV infected patients on antiretroviral therapy. *PLOS One* 2013;**8**:e61949. http://dx.doi.org/10.1371/journal.pone.0061949

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Appendix 1 Trial protocol

Protease Inhibitor monotherapy Versus Ongoing Triple-therapy in the long-term management of HIV infection

Full title: 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

EUDRACT: 2007-006448-23
ISRCTN04857074

Version 1.1, 25 March 2008

Authorised by:

Name:	Dr N Paton	Role:	Chief Investigator
Signature:		Date:	25th March 2008
Name:	Dr D Dunn	Role:	Trial Statistician
Signature:		Date:	25/3/2008

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GENERAL INFORMATION

This document describes the PIVOT trial and provides information about procedures for entering patients into the trial. The protocol should not be used as an aide-memoire or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the HIV Group, Medical Research Council Clinical Trials Unit, London, to confirm they have the most up-to-date version. Clinical problems relating to this trial should be referred to the Chief Investigator.

- **Compliance**
  The trial will be conducted in compliance with the protocol, MRC GCP, Data Protection Act (DPA number: Z5886415), NHS research governance and other regulatory requirements, as appropriate in the participating centres.

- **Sponsor**
  Medical Research Council, 20 Park Crescent Road, London W1B 1AL, UK.

- **Funder**
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For the listing of participating institutions and clinicians please refer to Appendix 4.

RANDOMISATION

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SUSAR NOTIFICATION

Within one working day of becoming aware of an SUSAR, please fax a completed SUSAR form to the MRC Clinical Trials Unit on:
Fax: +44 (0)20 7670 4817

CONTENTS

LIST OF FIGURES

LIST OF TABLES

APPENDICES

ABBREVIATIONS AND GLOSSARY

AE	Adverse event
ACTG	AIDS Clinical Trials Group
AIDS	Acquired immune deficiency syndrome
ALT	Alanine transaminase
AR	Adverse reaction
ART	Antiretroviral therapy
AST	Alanine aminotransferase
BHIVA	British HIV Association
BNF	British National Formulary
CCR5	Chemokine (C-C motif) receptor 5
CDC	Center for Disease Control and prevention
CDSC	Communicable Disease Surveillance Centre
CHM	Commission on Human Medicine
CF	Consent form
CG	Cockcroft-Gault equation
CI	Chief Investigator
CRF	Case Report Form
CT	Computerised (Axial) Tomography scan
CTA	Clinical Trials Authorisation
CTU	Clinical Trials Unit
DoH	Department of Health
ECG	Electrocardiogram (also EKG)
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-Linked ImmunoSorbent Assay
EQ-5D	Euroqol (five-domain) health status questionnaire
ERC	Endpoint Review Committee
EUDRACT	European Union Drug Regulatory Agency Clinical Trial
GP	General Practitioner
HAART	Highly Active Antiretroviral Therapy
HDL	High-density lipoprotein
HE	Health Economics
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
IB	Investigator's Brochure
HVLT-R	Hopkins Verbal Learning Test - revised
ICH GCP	International Conference on Harmonisation Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
ISRCTN	International standard randomised controlled trial number
ITT	Intention to treat
KS	Kaposi's sarcoma
LDL	Low-density lipoprotein
LFT	Liver function tests
LREC	Local research ethics committee
MHRA	Medicines and Healthcare Regulatory Authority

MHS	Mental health summary score
MI	Myocardial infarction
MOS HIV	Medical Outcomes Study HIV Health Survey
MRC	Medical Research Council
MRI	Magnetic resonance imaging
NARS	Neuropsychiatric AIDS Rating Scale
NHS	National Health Service
NRTI	Nucleoside reverse transcriptase inhibitors
NNRTI	Non-nucleoside reverse transcriptase inhibitors
OT	On-treatment
PHS	Physical health summary score
PI	Protease Inhibitor
PIS	Patient Information Sheet
QALY	Quality-adjusted life-year
QoL	Quality of Life
R&D	Research and Development
REC	Research Ethics Committee
RNA	Ribonucleic acid
SAE	Serious adverse event
SAR	Serious adverse reaction
SOP	Standard operating procedure
SmPC	Summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction
TLOVR	"Time to loss of virologic response"
TDM	Therapeutic drug monitoring
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected adverse reaction
UEC	Urea, Electrolytes and Creatinine
UK-CAB	United Kingdom Community Advisory Board
ULN	Upper limit of normal
VL	Viral load

1. SUMMARY

1.1 Background and Aims

The current standard-of-care treatment for people living with HIV is combination antiretroviral therapy (ART), usually consisting of 3 drugs: 2 nucleoside reverse transcriptase inhibitors (NRTIs) with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). Although triple ART has a relatively high long-term success rate, a proportion of patients (about 4% per year) continues to experience virological failure, and this is often associated with complete resistance to one or more drugs (especially NRTI and NNRTI classes). Furthermore, long-term drug toxicity remains a concern. Additional strategies for long-term management are needed that preserve future drug options and minimise toxicity. Short-term clinical trials suggest that stable patients who have had prolonged virological suppression on combination ART can be switched successfully to PI monotherapy, resulting in a reduction of toxicity without increasing the risk of treatment failure and drug resistance.

This trial aims to determine whether a strategy of switching to PI monotherapy is non-inferior to continuing triple-therapy, in terms of the proportion of patients who maintain all the drug treatment options that were available to them at baseline after at least 3 years of follow-up, and to compare clinical events, safety, toxicity and health economic parameters between the two strategies.

1.1.1 Trial design

This is a parallel group, open-label, multi-centre, randomised controlled strategy trial.

1.1.2 Patients to be included

400 patients will be included who are HIV-infected adults on a stable ART regimen of two NRTIs and one NNRTI or PI. Patients will have CD4+ T-cell counts greater than 100 cells/μL, and viral load (VL) less than 50 copies/ml for no less than 6 months. Patients who have previously failed on a PI-containing regimen, who have PI resistance mutations, or in whom PIs are contraindicated will not participate. For more details refer to section 4.

1.1.3 Trial interventions – research and control arm

Patients randomised to the PI monotherapy group will stop other ART drugs and start or continue only on a ritonavir-boosted PI (selection of drug at discretion of physician and patient). Those who do not maintain complete virological suppression or who are unable to tolerate the PI (substitution for toxicity is allowed), will promptly switch back to their previous triple-therapy. Patients randomised to the control group will continue their current regimen. For more details refer to section 6.

1.1.4 Duration of trial

The trial will be conducted over 5 years, including an initial recruitment period estimated to last 12 to 18 months. All patients will continue on treatment and follow-up until close of the trial. For more details refer to section 7.

1.1.5 Outcome measures

Analyses will compare the 2 groups by intention to treat (ITT).

Primary outcome measure:

Loss of future drug options defined as the occurrence of intermediate to high level resistance to any one or more of the standard antiretroviral drugs (limited to licensed drugs in contemporary use) to which the patient's virus was considered to be sensitive at trial entry.

Secondary outcome measures:

- Serious drug or disease-related complications
- Adverse events
- Virological rebound
- CD4+ count change
- Health-related Quality of Life change
- Neurocognitive function change
- Cardiovascular risk change
- Health care costs

For more details refer to section 9.

1.1.6 Data recorded directly on CRFs

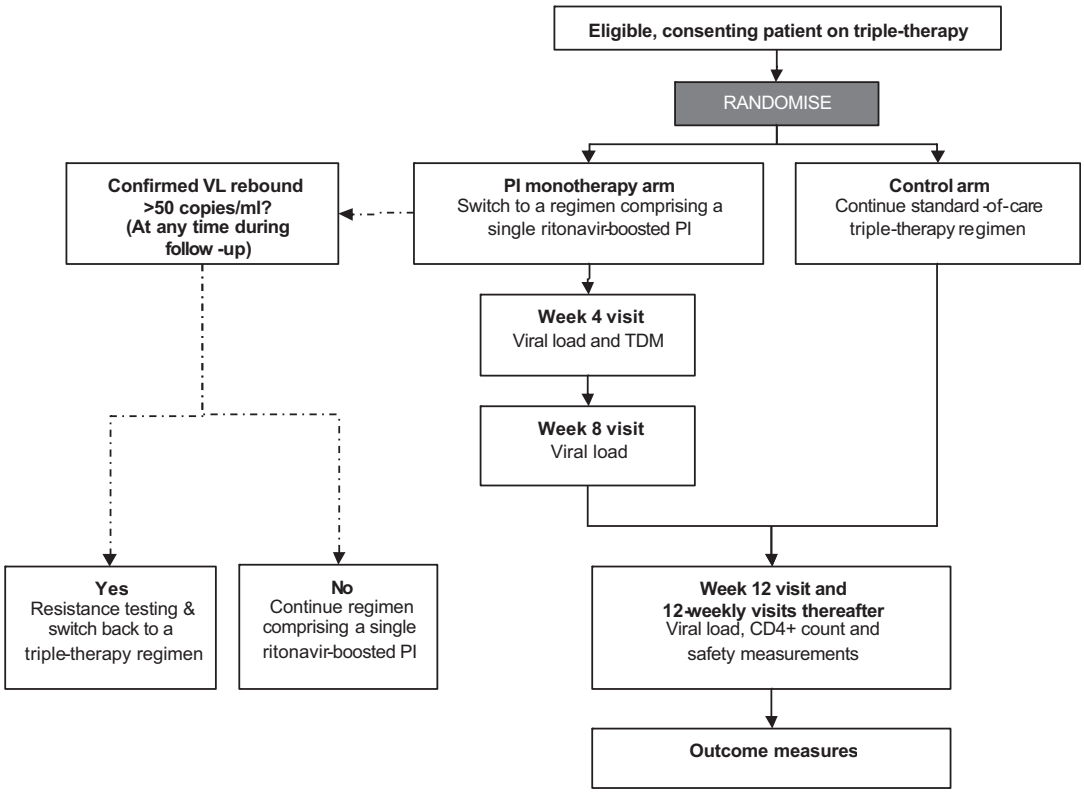
Clinical and routine laboratory data will be recorded on case report forms (CRFs). A copy will be faxed or sent to the MRC CTU for data entry and the original will be kept at the local centre. For more details see section 7.

1.1.7 Organisation

Sponsor: Medical Research Council, UK.
Funder: NHS R&D Health Technology Assessment (HTA) programme, UK.
Coordinator: Medical Research Council Clinical Trials Unit, UK.

1.2 Flow diagram

Figure 1: Trial entry, randomisation and treatment



1.3 Trial schedule

PIVOT trial schedule	Screening -4wks to Day 0	Day 0 (Baseline)	PI monotherapy arm only		Week 12 +/- 2 wks	Subsequent 12-weekly visits Wk 24, 36 etc +/- 4 wks	Annual visits Wk 48, 96, 144, 192, 240 and final visit[10] +/- 4 wks
			Week 4 +/-2 wks	Week 8 +/- 2 wks			
Complete and sign Consent Form	X						
Medical and drug history	X						
Assessment of drug adherence		X	X	X	X	X	X
Concomitant medication		X	X	X	X	X	X
Symptom review / physical examination	X	X	X	X	X	X	X
Assessment of clinical adverse events		X	X	X	X	X	X
Cardiovascular risk assessment	X						X
ECG (within last 6 months acceptable)	X						
Assessment of healthcare resource utilisation		X	X	X	X	X	X
EQ-5D health status questionnaire		X			X	X	X
Neurocognitive assessment		X			X		X
MOS-HIV questionnaire		X			X		X
HIV viral load[1,2]	X	X	X	X	X	X	X
CD4+ count	X	X			X	X	X
Full blood count[3]	X	X	X		X	X	X
UEC and LFTs[4]	X	X	X		X	X	X
Bone profile[5]	X				X[5]	X[5]	X
Glucose (fasting)	X		X		X		X
Lipids (fasting)[6]	X		X		X		X
Urine protein/creatinine ratio[5]	X				X[5]	X[5]	X
Hepatitis B/C serology (within last 6 months acceptable)	X						X
Pregnancy test[7]	X						
Plasma sample for storage[8]	X	X	X		X		X
PI drug concentration[9]			X	X[8]	X[8]		
Completion of CRF	X	X	X	X	X	X	X

1 HIV viral load will be repeated on the same lab sample for any value >50 copies/ml. If >50 copies/ml confirmed on lab re-test, patient will be telephoned for adherence counselling and asked to return for repeat VL test at 4 weeks (window up to 6 weeks) after the first test. Repeat plasma sample for storage will be obtained at the second visit.
2 Resistance testing will be performed on a stored sample at the local laboratory in the event of 2 consecutive VL values >50 copies/ml. Resistance testing will be performed on the higher of the two samples. If VL results differ by less than 50 copies/ml the second sample will be used for resistance testing.
3 FBC will include Hb, WCC, neutrophil count, lymphocyte count, platelets.
4 UEC will include sodium, potassium, urea, creatinine; LFTs will include bilirubin, ALT, alkaline phosphatase.
5 Bone profile (calcium and phosphate) and urine protein/creatinine ratio will be performed quarterly only if patients are taking tenofovir.
6 Lipids will include total cholesterol, triglycerides, LDL, HDL. If elevated at Week 12, additional fasting lipid tests can be performed between the annual visit checks as needed to inform clinical management.
7 Pregnancy test in women only; can be urine or blood test, as per standard practice at site; repeated at any subsequent visits where pregnancy is suspected.
8 Blood sample will be stored at these visits plus any visit where a second VL sample is taken for confirmation of rebound.
9 PI drug concentration measurement can be repeated at Week 8 and/or Week 12 if Week 4 concentration is low (only in the PI monotherapy arm).
10 The final visit will be scheduled within 12 weeks before the common closing date of the trial.

DOI: 10.3310/hta20210

2. BACKGROUND

2.1 Introduction

At the end of 2005 there were an estimated 63,500 people living with HIV in the UK, of whom approximately two-thirds have been diagnosed and seen for HIV-related care. The annual number of new HIV diagnoses made in the UK continues to rise, with 7450 new cases in 2005 (1), and as more people receive effective treatment, the number of deaths continues to fall. Thus the number of people receiving treatment and the already substantial burden on the NHS will continue for the foreseeable future.

A range of drugs are available that are active in blocking the replication of HIV. The current standard-of-care is the use of combination ART, usually consisting of 3 drugs: a backbone of 2 NRTIs with either a NNRTI or a PI. Such combination therapy has been shown to be effective in reducing viral load, preventing decline in immune function and dramatically decreases the risk of opportunistic infections and morbidity and mortality from HIV.

2.2 Managing HIV as a long-term chronic disease: changes in the treatment paradigm

The SMART study showed inferior outcomes with treatment interruption rather than continued ART, clearly demonstrating that ART needs to be continued indefinitely once it has been started (2).

Inference from the SMART data as well as consideration of cohort data has lead to a renewed debate on the possible merit of initiating ART even earlier in the course of disease than is currently the case (3). A major HIV therapeutic trial will soon commence to address the question of whether ART should be started at CD4+ counts above 500 cells/mm^3.

Consequent on the move towards extending therapy exposure (start earlier and continue indefinitely) is the realisation that patients are now facing the prospect of taking ART for decades. Considerations of maximising long-term durability, preserving a viable sequence of future drug options, and minimising long-term side effects are becoming increasingly important.

Much of the current pharmaceutical company driven research as well as investigator-initiated research is now designed to look at switching drugs or comparing regimens for toxicity or tolerability advantages. The search for cost-effective approaches to care, including ways of containing drug costs as well as looking at approaches to simplify monitoring and follow-up are also an important focus of current research. Several promising new drugs that act on different targets will soon be available (an integrase inhibitor and a CCR5 inhibitor) as well as better options of new drugs with potentially greater efficacy or reduced toxicity within existing classes. These new drugs will increase treatment options available, but will also lead to re-examination of the paradigm of care (treatment with triple-therapy, comprising 2 NRTIs and a NNRTI or PI) that has changed little in the last decade. The availability of more treatment options may also allow the flexibility to accept a small risk of treatment failure in a regimen that has fewer side effects or that effectively preserves long-term treatment options in the vast majority.

Thus research into more innovative uses of current drugs, as well as ways of combining or sequencing drugs to maximise long-term outcomes (preserving viable treatment options, minimising toxicity, minimising cost) will become increasingly important. Given that

treatment interruption is not a sensible option, (2) treatment simplification studies form an increasingly important aspect of the HIV treatment research agenda. The most promising candidates for treatment simplification are undoubtedly the PIs.

2.3 Previous trials of PI monotherapy

Four randomised controlled trials of PI monotherapy were presented as abstracts at the 16th World AIDS Conference in Toronto in August 2006, two of which have been recently published in full in a peer-reviewed journal. Three of these trials investigated switching to lopinavir monotherapy after patients had gained full virological suppression using triple-therapy. The largest of these studies, OK 04, enrolled 205 patients who were stable on triple-therapy and randomised them to switch to triple-therapy with lopinavir, or lopinavir monotherapy. Monotherapy was found to be non-inferior (defined with a non-inferiority margin of 12%) to triple-therapy at 48 weeks based on proportion with VL >500 copies/ml. The majority of patients (89%) maintained viral suppression without the need for re-induction and only two patients in this study developed primary PI mutations (4). The data for 96 weeks of follow-up were presented at the European AIDS Conference in October 2007, and showed that lopinavir monotherapy continued to be non-inferior to continuing triple-therapy, with no further virological rebounds with PI resistance. The percentage of patients without therapeutic failure was 87% in the monotherapy arm and 78% in the triple-therapy arm, and there were significantly fewer adverse events in the monotherapy arm (5). In the second study (M03-613) presented in Toronto, 155 treatment-naïve patients were randomised to induction with 2 NRTIs plus lopinavir, followed after 6 months by lopinavir monotherapy versus standard-of-care 2 NRTIs and a NNRTI. There was no significant difference in the rate of maintaining VL <50 copies/ml in the two groups through 96 weeks. Although intermittent increases in VL were seen often in the monotherapy arm, most returned to <50 copies/ml spontaneously and only 4 patients required re-introduction of NRTIs. Two patients treated in the monotherapy arm developed PI resistance mutations (6). The third study, KalMo, randomised 60 patients on stable combination therapy and with undetectable VL to continue existing ART or to receive lopinavir monotherapy. There was no difference in the proportion of patients who maintained undetectable VL in the two groups at 48 weeks (83% in standard-of-care and 86% in monotherapy), and none of the patients in the PI monotherapy arm developed resistance mutations (7). Taken together these 3 randomised controlled trials suggest that switching to lopinavir monotherapy is a viable treatment option in patients who have been already established on stable triple-therapy.

In contrast, the fourth study compared lopinavir monotherapy with triple-therapy in treatment naïve patients starting therapy for the first time and found a high proportion of patients had low level viraemia in the monotherapy arm and the on treatment analysis showed an inferior response in the monotherapy arm (8). Based on this limited data, it appears as though PI monotherapy may be more valuable when used as a switch strategy rather than as first-line therapy in treatment naïve individuals.

Although the randomised controlled trials to date have all been performed with lopinavir, other PIs may be effective in maintaining viral suppression when used as monotherapy. In a non-randomised trial, ACTG 5201, 33 patients who had achieved undetectable VL on triple-therapy with boosted atazanavir, discontinued nucleosides and remained on atazanavir monotherapy. At week 24, 3 patients had virological rebound, one of whom re-suppressed spontaneously on monotherapy. The other 2 patients had undetectable blood atazanavir levels and were presumably non-adherent to treatment. None of the patients developed resistance mutations to atazanavir (9). In a non-randomised trial conducted in Sweden, 5 of 15 patients who switched from stable triple-therapy (either an NNRTI-based or triple NRTI regimen) to boosted atazanavir monotherapy had VL rebound between weeks 12 to 16 (2 samples above 20 copies/ml) (10). The high proportion of patients who experienced rebound

may perhaps be explained by residual CYP3A4 enzyme-inducing effects of NNRTI reducing atazanavir levels in the period immediately following the switch, which might be avoided by continuing the NRTIs for the first few weeks (11). The study has also been criticised because two of the patients that failed used acid-suppressing drugs (ranitidine and lansoprazole) which are known to decrease atazanavir levels and were specifically contraindicated in the protocol (11). Of note, none of the 5 patients with VL rebound developed PI resistance, and all re-suppressed VL with re-introduction of triple-therapy (10).

There are currently two ongoing randomised controlled trials and one ongoing uncontrolled trial investigating PI monotherapy for patients who have achieved undetectable VL on existing treatment. The highly-active ART (HAART) followed by maintenance with monotherapy - Kaletra study (MAIMOKA study; ISRCTN45284754) is comparing lopinavir monotherapy to standard-of-care triple-therapy for patients who have achieved undetectable VL on treatment. The recruitment target is 240 patients with an anticipated study end date of October 2008. The primary endpoint is therapy failure (defined as VL >400 copies/ml) at 96 weeks. A phase III study of darunavir monotherapy is currently underway, and will randomise 250 patients with undetectable VL on triple-therapy to take darunavir alone, or take triple-therapy including darunavir (NCT005 13513). The primary endpoint is maintained suppression of VL <50 copies/ml at 48 weeks. The study is designed as a non-inferiority study (12% margin), and will report at end 2008/ early 2009 (12).

The Only REYataz (OREY) study (NCT00337467) is an uncontrolled study of atazanavir monotherapy in 62 patients who have achieved undetectable VL on their previous combination therapy. The primary endpoint is the proportion of patients who have virological rebound at Week 48.

2.4 Rationale and objectives of this trial

2.4.1 Why is this long-term strategy trial needed?

Although the trials of PI monotherapy described above are encouraging, this research is driven by the pharmaceutical industry with a typical short-term focus. A definitive trial focused on long-term outcomes is lacking. This trial is different in a number of respects from the previously completed or ongoing pharma-sponsored studies:

(i) Whereas other studies examine the effect of PI monotherapy *per se*, this trial will examine the effect of a *strategy* that includes prompt switch back to standard-of-care when PI monotherapy does not maintain full virological suppression of <50 copies/ml.

(ii) Whereas previous or ongoing studies are focused on specific PI drugs and specified comparator regimens, this trial allows drug selection according to patient/ physician preference and selection or switching of PIs for maximising tolerability; it is therefore more relevant to clinical practice.

(iii) Whereas other studies are of relatively short duration of one to two years, this trial has relatively long-term follow-up (up to 5 years) which is important for assessing long-term consequences of this strategy.

(iv) Whereas other studies focus on short-term VL endpoints (reflecting their commercial origin and single drug focus), this trial has an endpoint of clinical drug resistance, chosen to be most relevant to the long-term goal of maintaining effective treatment regimens.

(v) This trial is of sufficient size and, therefore, power to answer questions reliably.

(vi) This trial will collect relevant health care utilisation data for determining cost implications.

It is very unlikely that there will be a pharma-initiated study looking at long-term use of this strategy, and the trial we propose is likely to be the definitive long-term randomised controlled trial that addresses this important strategic option for long-term HIV therapy.

The trial objectives are:

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

2. To compare the safety and toxicity of PI monotherapy with standard-of-care triple-therapy over 3 to 5 years.

3. To assess the health economic benefits of use of PI monotherapy.

2.5 Risks and benefits of the PI monotherapy strategy used in this trial

2.5.1 Risk of side effects from treatment

The patients recruited into this trial will be, by definition, stable on their current standard-of care treatment regimen of 2 NRTIs and an NNRTI or PI. Patients who are taking this regimen will, in general, be free from major side effects on this regimen, as they would have otherwise changed therapy prior to enrolment. Patients who are randomised to the intervention arm will in some cases start a new PI to which they have not been exposed previously. Although the PIs that are in contemporary use are in general well tolerated, there is a risk that some patients will experience new side effects from the selected PI. Side effects of PIs include gastro-intestinal disturbances (including diarrhoea, nausea, vomiting, abdominal pain, flatulence), anorexia, hepatic dysfunction, pancreatitis; blood disorders including anaemia, neutropenia, and thrombocytopenia; sleep disturbances, fatigue, headache, dizziness, paraesthesia, myalgia, myositis, rhabdomyolysis; taste disturbances; rash, pruritus, Stevens-Johnson syndrome, hypersensitivity reactions including anaphylaxis, metabolic disturbances such as hyperglycaemia, hypertriglycerideaemia and hypercholesterolaemia and visceral fat accumulation.

A recent epidemiological study identified an association between treatment with a PI and the risk of myocardial infarction, although the effect appears modest (relative risk per year of exposure 1.16) especially when compared to the risks associated with other cardiovascular risk factors (increasing age 1.39; male sex 1.91; current smoking 2.83; history of cardiovascular disease 4.3) (13) (14). The association between PI treatment and risk of myocardial infarction was further reduced by adjusting for serum lipid levels. The overall incidence of myocardial infarction in patients exposed to PI treatment for more than 6 years was only 0.6% per year, which is small. To address this issue, this trial will include formal assessment of cardiovascular risk as part of the screening criteria, and will not enroll patients with very high level of background risk. Lipid levels will be measured periodically, and clinicians will be encouraged to manage lipid elevations fastidiously according to current BHIVA treatment guidelines. The protocol also allows switching to other protease inhibitors, some of which have minimal effects on lipid levels. Other modifiable risk factors (e.g. high blood pressure and diabetes) will also be sought actively and managed according to

guidelines, and patients who smoke will be encouraged to stop. With these measures, any increased risk of myocardial infarction in those patients who switch to a protease inhibitor for the first time is expected to be very low.

The PIs used in the trial will all be licensed drugs which have been used in many thousands of patients with HIV disease. Therefore risk of adverse events is quantifiable and known to be relatively small. Furthermore, the inclusion and exclusion criteria identify patients at risk of metabolic problems and more serious side effects and such patients will not be enrolled into the trial. Physicians and patients will be allowed to select the PI best suited to that patient, and, if necessary, to switch to an alternative PI if there are tolerability or toxicity problems. Patients will be monitored carefully during the intervention for known and unknown side effects of PIs allowing effective and appropriate management of these effects. Lastly, the protocol allows switch back to triple therapy (with or without a PI) in the event of unmanageable toxicity occurring in the PI monotherapy arm.

2.5.2 Risk of virological failure with resistance

There is a risk of virological failure with development of resistance. Patients selected for participation in this trial will be stable on their current standard-of-care regimen, with a relatively low probability of treatment failure in the long-term. Patients who are randomised to the intervention arm will have standard-of-care triple-therapy changed to PI monotherapy. Based on studies to date, it is likely that a small proportion of patients will not maintain full viral suppression on PI monotherapy, and if not addressed, there is the risk that ongoing viral replication may lead to the development of resistance mutations. In order to minimise the risk of developing resistance, patients who are known to have resistance to PIs or who have any evidence of failure on a PI-containing regimen will not be included. Most patients in the UK are now tested for resistance prior to starting therapy, but in those who have not been tested the risk of harbouring transmitted PI resistance is low (1.8% in 2005, data obtained from the UK HIV Drug Resistance Database) and so it is not a major concern if a baseline test was not done. Thus patients in the intervention arm should enjoy the full activity of the PI monotherapy. The fact that the trial is recruiting patients with stable undetectable VL (as opposed to initiating patients on PI monotherapy) means that patients will not be exposed to high levels of viral replication when they start the PI (hence the risk of developing *de novo* resistance is very low). Furthermore, patients will be monitored closely in the initial three months after treatment switch with regular VL testing, and patients who do not maintain virological suppression will be switched back promptly to triple-therapy. The protocol also includes early therapeutic drug monitoring as an additional safety measure to identify patients who have inadequate drug levels to maintain viral control. Given these conditions, it is very unlikely that patients will develop significant resistance to the PI even if they experience a short period of low level viral replication between the protocol-mandated testing points.

There is a small risk that patients who do not successfully maintain virological suppression on a regimen of PI monotherapy may fail to re-suppress even if standard-of-care triple-therapy is re-introduced. However, if re-induction is required it will likely be from a starting point of relatively low level of viral replication on PI monotherapy, and the re-introduction of standard-of-care triple-therapy in this situation is unlikely to be associated with significant risk of new mutations developing in the triple-therapy regimen. The previous PI monotherapy studies described above all report successful re-induction in patients who are not fully suppressed with PI monotherapy. The largest of these studies, OK 04, that adopted a less stringent protocol for switching back to triple-therapy than the one used in this study, found no excess resistance developing in the PI monotherapy arm (15).

In the studies of Kaletra monotherapy reported to date, virological failure has been almost entirely related to poor adherence. We anticipate that there will not be major problems with adherence in this trial. The trial will recruit HIV-infected patients who have been established

on ART for at least 6 months and will, in most cases, have been taking therapy for many years. Such patients have been repeatedly counselled about the importance of achieving and maintaining a high level of adherence to therapy, since this is known to be essential for successful HIV treatment. We will be recruiting patients who have had consistently undetectable VL measurements, and thereby selecting patients who have demonstrated an ability to sustain high levels of treatment adherence.

2.5.3 Risk of viral rebound in the genital compartment and increased HIV transmission

Whereas NRTIs are concentrated in genital secretions, and NNRTIs reach approximately the same concentration as in plasma, the concentration of PIs in genital secretions is variable and not fully known for the newer PIs (16). There is therefore a risk of sub-optimal drug levels, ongoing viral replication and development of resistance in the genital tract with PI monotherapy, even though plasma VL may be rendered undetectable. For the minority of individuals who are not practising safe sex, there will also be a theoretical risk of transmitting the resistant virus to others.

2.5.4 Risk of viral rebound in the central nervous system and neurocognitive decline

The penetration of PIs into the central nervous system (CNS) is variable and generally inferior to that of the other main drug classes. However, it appears that control of plasma viral replication is usually sufficient to control viral replication in the CNS. Furthermore, treatment with drug regimens that have limited CNS penetration does not appear to be associated with poor neurocognitive performance (17). One small study that measured VL in the cerebrospinal fluid in patients taking PI monotherapy (boosted atazanavir) found that 3 out of 20 patients had elevated VL in CSF despite VL suppression in plasma (18). This raises the theoretical concern that monotherapy (with some or all of the PIs) may lead to decline in neurocognitive function in a proportion of patients over time, although this has not been reported in any of the trials conducted to date. In this trial we will exclude patients who have evidence of significant neurocognitive impairment at screening, and neurocognitive function will be monitored throughout the study. If a patient shows evidence of decline in neurocognitive function they will be able to switch back promptly to triple therapy.

2.5.5 Benefits for trial participants and society

The benefits for trial participants who are randomised to take PI monotherapy are that they may have a reduced risk of long-term toxicity by using PI monotherapy (due to cessation of NRTIs and, in some cases, NNRTIs), a possible reduced risk of long-term failure because of the high genetic barrier to resistance (compared with NRTIs and NNRTIs), and a better profile of preserved drug options for the future. This counterbalances the small risk from new PI toxicity or development of resistance during viral load rebound as described above. All participants may benefit from the rigorous standard-of-care and increased attention to detail that are associated with participation in a clinical trial, and may appreciate some of the additional clinical measurements that are conducted as part of the trial (e.g. neurocognitive and quality of life assessments).

The benefits of the trial for society are that it may demonstrate the effectiveness of using PI monotherapy as treatment strategy, thereby increasing the number of strategies available for the long-term management of this chronic disease. This will represent an improvement in the care of HIV infected individuals. The trial may also identify a more economical approach to therapy and, in a setting of a healthcare system with finite resources; this would in turn benefit society by freeing up resources that could be deployed to other aspects of HIV care, or to other disease areas.

3. SELECTION OF CENTRES & CLINICIANS

The trial will be conducted at approximately 40 sites in the UK and 4 international sites. A list of the selected UK sites is shown in Appendix 4.

3.1 Criteria for selection of trial sites & clinicians

- The clinical trial ste is involved in the treatment of HIV patients.
- The site has the potential to recruit at least 10 patients within the 12-18 month recruitment period.
- The investigator has appropriate experience of conducting trials according to Good Clinical Practice.
- Clinical trial staff are familiar with the appropriate use of investigational products, as described in the protocol.
- The clinical trial site has an adequate number of qualified staff and adequate facilities, for the foreseen duration of the trial, to conduct the trial properly and safely.

3.2 Site responsibilities

- The site must have a signed written agreement between the Trust and the MRC that will outline details of the trial governance, obligations of parties, liabilities and indemnity.
- The site must conduct the trial in accordance with the current protocol and changes will only be made when necessary to protect the safety, rights and welfare of patients.
- The site must conduct the trial in compliance with the International Conference on Harmonisation (ICH) GCP and applicable regulatory requirements.
- The site must ensure that all staff assisting with the trial are adequately informed about the protocol and the investigational products and aware of their trial related duties.
- The site must permit monitoring and audit of source documentation. Direct access to all trial related sites documents, reports and data must be available.
- The site must maintain a trial master file, which contains all essential documents for the conduct of the trial.
- The site must submit all trial data in a timely manner, and as described in the protocol.
- The site must submit promptly all serious adverse events reports and follow-up with detailed written reports as appropriate.

- The site must not disclose any trial related data without the approval of the Trial Steering Committee.
- The site must retain all trial-related documents for 15 years after the completion of the trial.

3.3 Site approval

It is expected the site will submit the trial documentation for local research and development approval promptly, and at the latest 6 weeks following ethics approval. The site should begin trial-related screening activities no later than 4 weeks following the receipt of all necessary trial approvals and documentation.

A site initiation meeting with the MRC must occur before a site can be approved to randomise patients. The following documentation should be forwarded to the MRC CTU:

- Local research ethics committee approval of the protocol, patient information sheet and informed consent form, together with translations (if required).
- CV for Principal Investigator and co-investigators.
- Delegation of Authority log.
- Copy of local p harmacy dispensing SOP.
- Approval of the institution's local Research and Development office, if required.

For each clinical trial site, the responsibilities and contact details (phone, fax and email address) of each person working on the trial must be documented on the Delegation of Authority log. Clinical trial sites must notify the MRC CTU of any subsequent changes to trial personnel and/or their responsibilities. A current copy of the log must be stored in the trial master file at the clinical trial site and also at the MRC CTU.

4. SELECTION OF PATIENTS

Patients will be considered eligible for enrolment in the trial if they fulfil all of the inclusion criteria and none of the exclusion criteria defined below.

4.1 Patient inclusion criteria

1. Documented HIV infection on ELISA and confirmatory test.

2. Male or female patients, aged 18 years or more.

3. Receiving combination ART for at least 24 weeks with a regimen comprising 2 NRTIs and either an NNRTI or a PI (boosted or un-boosted).

4. No change in ART drugs in the 12 weeks prior to screening.

5. Plasma VL <50 copies/ml for at least 24 weeks prior to screening (must have at least 1 documented result <50 copies/ml at more than 24 weeks prior to screening, and at least 1 documented result <50 copies/ml taken within 12 weeks prior to screening). A patient who has had one VL "blip" to <200 copies/ml in the 24 weeks prior to screening may be included, provided that the 2 VL tests that immediately preceded the blip and the 2 VL tests that immediately followed the blip all gave results <50 copies/ml.

6. CD4+ count >100 cells/mm^3 at screening.
   This criterion is included because immune reconstitution is a priority in patients with very low CD4+ counts, and there is currently insufficient data to assess whether PI monotherapy will lead to equivalent rates of CD4+ recovery as standard-of-care treatment.

7. Willing to continue unchanged or to modify, antiretroviral therapy, in accordance with the randomised assignment.

8. Likely to be resident in the UK for the full duration of the trial and willing to comply with trial visit schedule throughout the follow-up period.

9. Willing to provide written informed consent.

4.2 Patient exclusion criteria

1. Known major protease resistance mutation(s) documented on prior resistance testing if performed (prior resistance testing is not mandatory for trial participation).

2. Evidence of previous failure while taking a PI-containing regimen (defined as failure to achieve VL <50 copies/ml within 24 weeks after starting a PI-containing regimen, or having 2 VL >50 copies/ml after having achieved a VL <50 copies/ml on the PI-containing regimen).
   This criterion is included to avoid pre-existing PI resistance that might compromise efficacy of PI monotherapy.

3. Evidence of previous failure on an NNRTI-containing regimen (defined as in 2, above), unless a successful viral sequence (resistance test) was obtained following failure and within 60 days prior to the date of switching to a new fully suppressive regimen.
   This criterion is included to minimise the chances that patients enter the trial with unrecognised/undocumented drug resistance which would diminish the accuracy of determining the primary endpoint of new drug resistance, should rebound occur during the trial.

4. Previous allergic reaction to a PI.

5. Patient currently using or likely to require use of concomitant medication with known interaction with PI s including rifampicin, amiodarone, flecainide, bupropion, clozapine, ergotamine, mexilitine, midazolam, pethidine, pimozide, quinidine, sertindole, sildenafil, voriconazole, zolpidem, St John's Wort.

6. Patient requiring treatment with radiotherapy, cytotoxic chemotherapy, or is anticipated to need these during the trial period.

7. Treatment for acute opportunistic infection within 3 months prior to trial screening.

8. Pregnant or trying to become pregnant at the time of trial entry.

9. History of active substance abuse or psychiatric illness that, in the opinion of the investigator, would preclude compliance with the protocol, dosing schedule or assessments.

10. History of HIV encephalopathy with current deficit >1 in any domain of the Neuropsychiatric AIDS Rating Scale (see Appendix 8).

11. Past or current history of cardiovascular disease, or 10 year absolute coronary heart disease risk of >30% (calculated from the Framingham equation (19), and assessed using the Joint British Societies cardiovascular risk prediction charts, Appendix 11).

12. History of insulin-dependent diabetes mellitus.

13. Patient currently receiving interferon therapy for Hepatitis C virus infection or considered likely to need such therapy during the course of the trial.

14. Co-infection with hepatitis B, defined as Hepatitis BsAg positive at screening or at any time since HIV diagnosis.
    This criterion is included to avoid the risk of a flare of Hepatitis B with NRTI withdrawal.

15. Any other active clinically significant condition, or findings during screening medical history or examination that would, in the opinion of the investigator, compromise the patient's safety or outcome in the trial.

16. Anaemia (haemoglobin <9.5g/dl), neutropenia (absolute neutrophil count <1000/mm^3) or thrombocytopenia (platelet count <50,000 /mm^3) at trial screening.

17. ALT or alkaline phosphatase greater than 3 times the upper limit of normal at trial screening.

18. Fasting plasma glucose >7.0mmol/L at trial screening.

19. Fasting plasma triglyceride level >3mmol/L at trial screening despite the use of lipid lowering drugs.

20. Fasting plasma total cholesterol >6.2mmol/L at trial screening despite the use of lipid lowering drugs.

4.3 Screening procedures and pre-randomisation investigations

4.3.1 Pre-screening check

Prior to the screening visit, a check of medical and drug history should be performed to ensure that the patient meets the basic medical eligibility criteria. Patients will be given adequate information about the trial together with a Patient Information Sheet (see Appendix 1) and given an opportunity to ask questions about the trial.

4.3.2 Screening visit

Potentially eligible individuals can be screened between 1 and 4 weeks before trial entry (i.e. Week -4 to Day 0) but results from the screening must be available prior to randomisation. The screening visit will be scheduled to occur in the morning due to the need for fasting blood tests. Patients should be instructed to not eat or drink anything (except plain water) from midnight before the visit, although they may take any necessary routine medication.

At the screening visit patients will be asked to verify that they have read the Patient Information Sheet and will be given a further opportunity to ask questions about the trial. If the patient is willing to proceed, the patient and Investigator must both sign 3 copies of the main trial Consent Form (see Appendix 2) (one copy to be given to the patient, one copy for the patient's clinic notes and one copy for the trial file) before any trial-specific screening procedures are carried out. All individuals screened must have their name, date of birth and clinic number recorded in the Trial Register against the next available trial number. This will then become their allocated trial number. The Trial Register must be stored by the investigator in a secure place only accessible to appropriate clinic staff. If an individual is not subsequently randomised the reason should be recorded in the register.

Screening assessments will be performed as listed below and as summarised in the trial schedule (see section 1.3):

- Review of medical history (including previous and current clinically important diseases and medications) and recording demographic information
- Review of symptoms
- Physical examination (including measurement of blood pressure)
- Assessment of cardiovascular risk factors and estimation of 10 year absolute coronary heart disease risk using charts based on the Framingham equation(19).
- Resting 12-lead electrocardiogram (ECG). The results of an ECG performed during the previous 6 months will be acceptable, provided that the printout is filed and available for review in the patients' case record. The ECG may be performed on or after the day of screening, but results must be available at the randomisation visit which needs to occur within 4 weeks following the screening visit.
- Laboratory tests:
  - HIV viral load
  - CD4+ count
  - Full blood count (haemoglobin, white cells, neutrophils, lymphocytes and platelets)
  - Biochemistry (sodium, potassium, urea, creatinine, bilirubin, ALT, alkaline phosphatase)
  - Bone profile (calcium, phosphate)

- Fasting glucose
- Fasting lipids (total cholesterol, triglycerides, LDL, HDL)
- Urine protein / creatinine ratio
- Hepatitis B surface antigen test and hepatitis C antibody test. The results of tests performed during the previous 6 months will be acceptable
- Urine (or serum) pregnancy test for women of childbearing potential
- Plasmastorage (2 X 4ml EDTA tube)

5. RANDOMISATION & ENROLMENT

5.1 Randomisation visit (Baseline; Day 0)

The randomisation visit should be scheduled for 1-4 weeks following the screening visit, but the results of all the screening assessments (including ECG) must be available prior to randomisation. There is no requirement for fasting at this trial visit.

For trial entry, all eligibility criteria must be fulfilled. These include the results of the evaluations carried out at screening which must be reviewed prior to the randomisation to make sure that the patient meets the criteria for trial entry. The research team should confirm that the patient continues to consent to enter the trial. The patient will be advised to inform their general practitioner of their trial participation, but this will not be a pre-requisite to enrolment. If the patient consents for their GP to be informed about participation (see Appendix 2) a letter should be sent to the GP (see Appendix 3).

Baseline assessments will be performed as listed below and as summarised in the Trial Schedule (see section 1.3).

- Review of medical and drug history since the screening visit
- Review of symptoms
- Review of concomitant medications
- Adherence to ART (patient will be asked about the number of missed doses in the previous 2 weeks, and in the previous 3 months)
- Targeted physical examination (as needed to evaluate symptoms; at this visit will include measurement of blood pressure, body weight, waist and hip-circumference, assessment of facial lipoatrophy and peripheral neuropathy)
- Neurocognitive assessment
- Review of healthcare resource utilisation (covering 3 months prior to randomisation visit) by patient self-report and review of case sheet
- MOS-HIV quality of life questionnaire (self-completed by patient)
- EQ-5D health status questionnaire (self-completed by patient)
- Laboratory tests:
    - HIV viral load
    - CD4+ count
    - Full blood count (haemoglobin, white cells, neutrophils, lymphocytes and platelets)
    - Biochemistry (sodium, potassium, urea, creatinine, bilirubin, ALT, alkaline phosphatase)
    - Plasma storage (1 X 4ml EDTA tube)

5.2 Procedure for randomisation

To randomise a patient the completed randomisation pages of the CRF must be faxed to the MRC CTU while the patient is present in the clinic.

RANDOMISATION

Tel: +44(0)20 7670 4843 (Mon - Fri, 09:00 – 17:00)
Fax: +44(0)20 7670 4817

Eligibility will be checked and if there are queries regarding the CRF the MRC CTU will contact the site by phone. Randomisation will be performed using a computer-generated randomisation list and the details of the patient's treatment allocation will be notified to the trial team at the site by fax and by phone within one hour of the receipt of the randomisation form. The patient's trial number, treatment allocation and the date of randomisation will be entered into the Trial Register at the MRC CTU, and these details should also be entered into the Trial Register at the site.

5.3 Post-randomisation procedures and follow-up

The clinician will complete a prescription with the patient's details and trial medication as allocated. The prescription will be for 3 months, or until the next protocol-mandated trial visit (see section 6.4).

Trial visit schedules will be sent by email or fax to the site at the time of randomisation. Patients should be followed on the same schedule even if their trial medication is discontinued. The target dates for trial visits are determined by the date of randomisation and are not affected by subsequent events. The schedule defines visit dates (with windows) necessary for data collection, but the patient may be seen more frequently for clinical care as needed.

Patients will also be given a card with the contact details for the trial research team.

Patients in the PI monotherapy arm will be asked to return in 4 weeks (visit window ±2 weeks). The Week 4 visit should be scheduled for the morning, and patients should be instructed not eat or drink anything (except plain water) from midnight before the visit. They should also be instructed to omit any morning dose of PI medication, and bring the medication with them to the clinic. They may take any other necessary dose of routine medication as usual.

Patients randomised to continue triple-therapy will be asked to return in 12 weeks. The Week 12 visit should be scheduled for the morning, and they should be instructed not eat or drink anything (except plain water) from midnight before the visit. They may take all their medication as usual.

5.4 Co-enrolment guidelines

Patients may not participate in any other clinical intervention trial while on this trial. Participation in other trials that do not involve an intervention may be permitted, but this should be discussed first with the Chief Investigator of this trial.

6. TREATMENT OF PATIENTS

6.1 Introduction

Patients will be randomised to a strategy of switching to a regimen comprising a single ritonavir-boosted PI or continuing triple drug therapy.

6.2 Control arm

Patients randomised to the control arm will continue to take their standard-of-care triple-therapy regimen. They will have regular viral load and other safety monitoring according to the standard-of-care as described in the assessment section and schedule of assessments table (VL testing every 12 weeks).

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.

6.3 PI monotherapy arm

6.3.1 Commencing PI monotherapy

Patients who are receiving an NNRTI-based regimen at baseline will discontinue the NNRTI and start a single ritonavir-boosted PI immediately following the randomisation visit. The two NRTIs will continue for a further 2 weeks after randomisation and then stop, so that from that point the patient will take only PI monotherapy. Consideration should be given to prescribing anti-diarrhoeal medication (e.g. loperamide) for the initial period of following PI initiation, if considered clinically appropriate to do so.

Patients who are receiving a PI-based regimen at baseline will discontinue the two NRTIs immediately following the randomisation visit. They will continue on a single ritonavir-boosted PI only, which may be the same or a different PI from the one they were taking at baseline.

6.3.2 Choice of protease inhibitor

This is a strategic trial and hence the choice of protease inhibitor will be left to physician and patient discretion. Any licensed, ritonavir-boosted PI will be permitted. Switches to alternative PIs will be 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.

The trial team at the MRC CTU will endeavour to provide investigators with relevant information, updates and any data from other trials of PI monotherapy that enters the public domain during the course of this trial so that investigators may use these to guide their choice of protease inhibitor monotherapy.

Any change in PI should be followed by a viral load at 4 weeks to verify that undetectable viral load is maintained.

6.3.3 Dose adjustment usin g therapeutic drug monitoring

A blood sample will be taken at Week 4 for measurement of the concentration (as close as possible to a trough level) of the PI (see section 7.3.1), and the results will be made available to the treating clinician prior to the Week 8 trial visit. The drug levels will be compared with the concentration-based cut-off values for efficacy (C_{trough}) given in international guidelines (20):

- Atazanavir 150 ng/mL
- Fosamprenavir 400 ng/mL
- Indinavir 100 ng/mL
- Lopinavir 1000 ng/mL
- Nelfinavir 800 ng/mL
- Saquinavir 100 ng/mL
- Tipranavir 20500 ng/mL

The cut-off value for darunavir will be taken as 550 ng/mL based on protein binding corrected EC50 in-v itro (21).

If the concentration of the PI is below the specified threshold, adjustments to the dose of the PI, the boosting dose of ritonavir, or the dose frequency may be made if thought to be clinically appropriate by the treating physician. The possibility of drug interaction with any concomitant medication the patient may be taking should also be considered prior to dose adjustment (see section 6.6). Expert advice will be available to the treating physician from the trial research team that includes an experienced clinical pharmacologist. All requests for such advice will be directed through the MRC CTU. If the P I concentration is below the stated threshold at week 4, up to 2 further therapeutic drug monitoring assays may be performed up to week 12, either to re-check a borderline low concentration, or to re-check the concentration after dose adjustment.

6.3.4 Virological monitoring and switching strategy

Patients in the PI monotherapy strategy arm will have VL testing performed at Weeks 4, 8 and 12, and every 12 weeks thereafter (see trial schedule, section 1.3). Additional VL testing will be performed in the event of a confirmed virological rebound, as described in section 7.2.1.

Patients who develop virological rebound after switching to PI monotherapy (defined as 2 consecutive VL values above 50 copies/ml taken 4-6 weeks apart, with the first being confirmed by a repeat assay on the same sample) will switch promptly back to a triple-therapy regimen. Exceptionally, upon receiving the second detectable VL result investigators may choose to switch to an alternative PI drug or dosing schedule if they consider that there is a strong chance that VL control could be re-established rapidly (e.g. by switching from once daily to twice daily PI). A further VL must be obtained within 4 weeks of this switch, and if this is detectable, patients must switch back to triple-therapy immediately.

6.3.5 Strategy for stopping or interrupting treatment with PI monotherapy

In addition to the virological rebound criteria given above, patients may be withdrawn (temporarily or permanently) from treatment with PI monotherapy for any of the following reasons at the discretion of the investigator:

- Disease progression while on therapy
- Unacceptable toxicity (e.g. insulin dependent diabetes developing *de novo*)
- Need for concomitant medication that has known interactions with the PI (and that cannot be avoided by switching to an alternative PI)
- Serious intercurrent illness or any change in the patient's condition which justifies the discontinuation or interruption of treatment in the clinician's opinion

- Pregnancy
- Patient withdraws consent

PI monotherapy should be resumed as soon as possible, if considered clinically appropriate to do so (e.g. toxicity resolves, patient is no longer pregnant, or requirement for contraindicated concomitant medication ends).

6.3.6 Strategy for switching back to triple-therapy

In the event that triple-therapy needs to be resumed, this should be the regimen that the patient was taking at trial entry. However, alternatives will be allowed if there is a strong preference for choosing alternative drugs (e.g. patients may have experienced relief from efavirenz-related neuropsychiatric side effects and may wish to continue on the PI), if there is a good clinical reason why change is indicated, or if the results of any resistance tests performed suggest that a particular combination would be preferable to that originally taken at baseline.

After returning to triple-therapy, changes of drugs can be made for subsequent virological failure or drug related toxicity as clinically indicated. Patients will be expected to remain on the strategy of receiving triple-therapy for the remaining duration of the trial, unless the interruption was temporary for one of the reasons listed in section 6.3.7. Resumption of PI monotherapy after a temporary suspension should be followed by VL testing after 4 weeks.

6.4 Management of drug toxicity and adverse events

Toxicity will be managed in both arms according to standard clinical practice. Wherever possible, any side effects will initially be managed by symptomatic measures and administration of appropriate (non-contraindicated) medication. In particular, Grade I-II gastrointestinal side effects such as nausea (with or without vomiting), and diarrhoea will be managed by anti-emetics and or antidiarrhoeal agents in the first instance. See Appendix 7 for details of toxicity grading. Interruption of or changes in ART will be avoided except in the event of Grade III or IV toxicity that is considered at least possibly related to one or more of the ART drugs. Wherever possible, alternative ART drugs will be selected that maintain the patient's randomised treatment strategy.

6.5 Management of cardiovascular disease risk factors

Cardiovascular risk factors (smoking status, blood pressure, fasting serum lipids and glucose) will be evaluated at baseline and annually during the trial.

At each of these annual assessments patients who report that they continue to smoke will be advised to give up smoking. This should be particularly emphasised in patients who have other factors that elevate cardiovascular risk. Patients who indicate that they are willing to attempt to stop smoking will be provided with contacts for smoking cessation programmes, or other counselling and assistance as appropriate.

Elevated blood pressure will be managed according to standard treatment guidelines.

Elevated lipid levels will be evaluated according to standard thresholds for treatment and managed according to current treatment guidelines. Management decisions should be based on fasted results. If elevated triglyceride or cholesterol results are obtained from a non-fasting blood sample, the test should be repeated after an overnight (10-hour) fast before management changes are instigated. Management will initially involve counselling to make appropriate changes in diet and exercise routine. Subsequently, if indicated, anti-

hyperlipidaemia medication may be used. If treatment with a statin is indicated, a drug that is not metabolised by the CYP3A4 pathway should be prescribed e.g. pravastatin (but consider possible interaction with darunavir), atorvastatin, or rosuvastatin (but consider possible interaction with lopinavir or darunavir). Up-to-date information on drug interactions should be sought (see reference sources in section 6.6, below). If these measures fail to provide adequate control of lipids, changes in ART may be considered (e.g. switching to an alternative PI or NNRTI that is considered to be less prone to cause hyperlipidaemia). Every attempt should be made to maintain the patient within the allocated treatment strategy and consideration should be given to discontinuing a PI only if lipid levels cannot be adequately controlled with these measures.

Diabetes will be diagnosed by standard approaches, and managed according to current best clinical practice. Management decisions should be based on fasted results. If elevated glucose levels are obtained from a non-fasting blood sample, the test should be repeated after an overnight (10-hour) fast before management changes are instigated. Management may involve initial referral for counselling and initiation of a diabetic diet, and prescription of oral hypoglycaemic agents. Switching to an alternative PI (or NNRTI) that is considered to be less prone to cause diabetes may be considered. Every attempt should be made to maintain the patient within the allocated treatment strategy and consideration should be given to discontinuing a PI only if the blood sugar cannot be adequately controlled with these measures. However, for patients who develop insulin dependent diabetes *de novo* following switching to a PI, it would be appropriate to consider early switching to an alternative ART regimen if available.

6.6 Concomitant medication

A large number of drugs have interactions with ART, and before prescribing any concomitant medication in this trial investigators should check with the drug interaction information listed in the current BNF (http://www.bnf.org) or current summary of product characteristics in the electronic medicines compendium (http://emc.medicines.org.uk), or with the detailed information on drug interactions provided in the University of Liverpool HIV drug interactions website (http://www.hiv-druginteractions.org).

In this trial, particular attention needs to be paid to avoid prescribing concomitant medications that are known to reduce PI drug levels, such as rifampicin, anticonvulsants, St John's Wort and acid-reducing agents. These interactions may differ between the individual PIs and the particular medications with drug classes, and details should be checked on the University of Liverpool HIV drug interactions website (http://www.hiv-druginteractions.org). A number of other medications may have serious interactions with one or more PIs, including warfarin, calcium channel blockers, ergot derivatives, benzodiazepines, and antifungals.

The latest summary checklist of PI drug interactions from the University of Liverpool HIV drug interactions website (http://www.hiv-druginteractions.org) will be sent to investigators at the start of the trial.

6.7 Drug supply, dispensing and accountability

Patients will be given a three month drug supply at each visit, corresponding to the protocol mandated frequency of follow-up. Prescriptions will be written on standard hospital forms, and drugs will be supplied from the hospital pharmacy. The local pharmacy dispensing SOP will be followed, including a record of the batch numbers of antiretroviral drugs dispensed.

6.8 Measures of adherence

Patients will be asked several simple questions regarding adherence (number of missed doses since last trial visit, number of missed doses in previous 2 weeks) as part of trial visits and the answers will be captured on the visit CRF.

7. ASSESSMENTS & FOLLOW-UP

7.1 Routine Follow-up

The trial will run for 5 years, with recruitment being completed within the first 12-18 months. All patients will continue follow-up to a common closing date.

The assessments are listed in the trial schedule (see section 1.3). Trial visits and assessments will correspond closely to routine clinical care, with 12-weekly visits throughout the trial. Patients randomised to the PI monotherapy arm will have additional visits at Week 4 and Week 8. Additional visits for VL testing will be required at 4-6 weeks following any confirmed VL rebound (see section 7.1.6). Data will be entered on the CRF at each visit.

7.1.1 Week 4

This visit is only required for patients randomised to the ***PI monotherapy arm.***

The visit window is ±2 weeks from the target visit date. The visit will be scheduled to occur in the morning due to the requirement for fasting blood tests. Patients should be instructed to not eat or drink anything (except plain water) from midnight before the visit. They should be instructed not to take any morning dose of PI medication (other medication can be taken) until after the blood has been drawn. The following assessments will be performed:

- Review of symptoms
- Review of concomitant medications
- Adherence to ART (no. of missed doses in previous 2 weeks and since last visit)
- Targeted physical examination (as needed to evaluate reported symptoms)
- Laboratory tests:
  - HIV viral load
  - Full blood count (haemoglobin, white cells, neutrophils, lymphocytes and platelets)
  - Biochemistry (sodium, potassium, urea, creatinine, bilirubin, ALT, alkaline phosphatase)
  - Fasting glucose
  - Fasting lipids (total cholesterol, triglycerides, LDL, HDL)
  - PI drug concentration (trough level preferred, or at least 4 hours from last dose)
  - Plasma storage (1 X 4ml EDTA sample)

7.1.2 Week 8

This visit is only required for patients randomised to the ***PI monotherapy arm.***

The visit window is ±2 weeks from the target visit date. The patient should be instructed not to take any morning dose of PI medication (other medication can be taken) until after they have been assessed in the clinic, in case a repeat PI drug level concentration may be required. If the trough level result at Week 4 is known to be above the threshold, then the patient can be instructed prior to the visit that the morning PI dose can be taken as scheduled (because a repeat drug concentration level will not be needed at Week 8). Adjustment to PI dose, ritonavir dose or drug schedule may be made at this visit depending on the results of PI levels measured at Week 4 (these will be available at this visit).

The required assessments at this visit are:

- Review of symptoms
- Review of concomitant medications

- Adherence to ART
- HIV viral load

Optional:

- PI drug concentration (trough level preferred, or at least 4 hours from last dose). This is only indicated if the Week 4 drug concentration was below the threshold and the clinician thinks it appropriate to recheck the level.

7.1.3 Week 12

This visit is required for ***all patients.***

The visit window is ±2 weeks from the target visit date. The visit will be scheduled to occur in the morning due to the requirement for fasting blood tests. Patients should be instructed to not eat or drink anything (except plain water) from midnight before the visit.

Patients on PI monotherapy arm who had a low PI concentration at Week 4 and for whom the clinician has decided that a further check on drug levels is warranted (for example if a dose adjustment has been performed at week 8) should be instructed not to take any morning dose of PI medication (other meds can be taken) until after the blood has been drawn. All other patients can take their morning medication as scheduled. The following assessments will be performed:

- Review of symptoms
- Review of concomitant medications
- Adherence to ART (no. of missed doses in previous 2 weeks and since last visit)
- Targeted physical examination (as needed to evaluate reported symptoms)
- Neurocognitive assessment
- Review of healthcare resource utilisation since last visit (patient self-report and review of case sheet)
- EQ-5D health status questionnaire (self-completed by patient)
- MOS-HIV quality of life questionnaire (self-completed by patient)
- Laboratory tests:
  - HIV viral load
  - CD4+ count
  - Full blood count (haemoglobin, white cells, neutrophils, lymphocytes and platelets)
  - Biochemistry (sodium, potassium, urea, creatinine, bilirubin, ALT, alkaline phosphatase)
  - Bone profile (calcium and phosphate; only required for patients taking tenofovir)
  - Fasting glucose
  - Fasting lipids (total cholesterol, triglycerides, LDL, HDL)
  - Urine protein / creatinine ratio (only required for patients taking tenofovir)
  - Plasma storage (1 X 4ml EDTA sample)

Optional:

- PI drug concentration (trough level preferred, or at least 4 hours from last dose). This is only indicated for patients in the PI monotherapy arm in whom the Week 4 drug concentration was below the threshold and for whom the clinician thinks it appropriate to recheck the level.

7.1.3 Subsequent 12-weekly visits (excluding "annual" visits and final trial visit)

These visits are required for ***all patients.***

The visit windows are ±4 weeks from the target visit date. There is no requirement for fasting or drug scheduling for these visits. The following assessments will be performed:

- Review of symptoms
- Review of concomitant medications
- Adherence to ART (no. of missed doses in previous 2 weeks and since last visit)
- Targeted physical examination (as needed to evaluate reported symptoms)
- Review of healthcare resource utilisation since last visit (patient self-report and review of case sheet)
- EQ-5D health status questionnaire (self-completed by patient)
- Laboratory tests:
  - HIV viral load
  - CD4+ count
  - Full blood count (haemoglobin, white cells, neutrophils, lymphocytes and platelets)
  - Biochemistry (sodium, potassium, urea, creatinine, bilirubin, ALT, alkaline phosphatase)
  - Bone profile (calcium and phosphate; only required for patients taking tenofovir)
  - Urine protein / creatinine ratio (only required for patients taking tenofovir)

7.1.4 "Annual" visits (week 48, 96, 144, 192, 240) and final trial visit

These visits are required for ***all patients.***

The visit windows are ±4 weeks from the target visit date. Patients should be instructed to not eat or drink anything (except plain water) from midnight before the visit. The following assessments will be performed:

- Review of symptoms
- Review of concomitant medications
- Adherence to ART (no. of missed doses in previous 2 weeks and 3 months)
- Targeted physical examination (as needed to evaluate reported symptoms; at this visit will include measurement of blood pressure, body weight, waist and hip-circumference and assessment of facial lipoatrophy; the final trial visit will also include an assessment of peripheral neuropathy)
- 10-year cardiovascular risk assessment
- Neurocognitive assessment
- Review of healthcare resource utilisation since last visit (patient self-report and review of case sheet)
- EQ-5D health status questionnaire (self-completed by patient)
- MOS-HIV quality of life questionnaire (self-completed by patient)
- Laboratory tests:
  - HIV viral load
  - CD4+ count
  - Full blood count (haemoglobin, white cells, neutrophils, lymphocytes and platelets)
  - Biochemistry (sodium, potassium, urea, creatinine, bilirubin, ALT, alkaline phosphatase)
  - Bone profile (calcium and phosphate; required for all patients at this visit)
  - Fasting glucose
  - Fasting lipids (total cholesterol, triglycerides, LDL, HDL)
  - Urine protein / creatinine ratio (required for all patients at this visit)

- Hepatitis B and C serology (if clinically indicated)
- Plasma storage (1x 4ml EDTA at annual visits; 2x 4ml EDTA at final trial visit)

7.1.5 Additional visits for virological rebound

These visits are required for ***all patients.***

In the event that the patient has a VL rebound >50 copies/ml, and this result is confirmed (by repeat laboratory testing on the same sample), an additional visit will be required and this should be scheduled to occur at 4-6 weeks following the date of the visit at which the sample with VL rebound was obtained.

For this repeat visit, patients in the PI monotherapy arm should be instructed not to take their morning dose of PI medication (other medications can be taken) until after the blood has been drawn. All other patients can take their morning medication as scheduled. The following assessments will be performed at this visit:

- Review of concomitant medications
- Adherence to ART (no. of missed doses in previous 2 weeks and 3 months)
- Laboratory tests:
  - HIV viral load
  - Resistance testing (store until VL test result available and only proceed if >50 copies/ml on the second sample)
  - Plasma storage (2x 4ml EDTA sample for later batched tests which may include PI drug levels)

If the second VL test shows an undetectable VL, follow-up will resume according to the next routine visit in the trial schedule. If the patient has another VL result >50 copies/ml later in the trial, the same procedure (re-run of the same sample, followed by repeat VL testing if confirmed detectable on the first sample) will be followed again.

7.1.6 Additional visits following ART change

This visit is required for ***all patients.***

For patients in either treatment arm who change therapy as a result of VL rebound, an additional visit should be scheduled at 4-6 weeks following the date of therapy change. Review of symptoms, concomitant medication and treatment adherence will be performed. The only required laboratory assessment at this visit is VL testing, but additional laboratory tests may be performed as clinically indicated. Follow-up should then resume according to trial schedule, but further unscheduled visits may be arranged if considered appropriate for clinical management.

7.2 Procedures for assessing efficacy

7.2.1 Viral load

VL testing will be performed at the local site laboratory with the standard assay for detecting low levels of VL that is routinely used at the site. The site laboratory will be required to demonstrate satisfactory participation in a recognised quality control program for VL testing.

Any VL result >50 copies/ml will be initially confirmed by re-testing the same sample on a separate laboratory run. If the result is confirmed as >50 copies/ml, the patient will be recalled for a repeat sample. This second assay need be run only once.

In order to be able to extrapolate the findings beyond the 5 year period of the trial, it will be important to document that the patients on PI monotherapy who remain virologically

suppressed during the trial have full virological suppression (to the same extent as patients on triple-therapy). Therefore, additional testing using a very low copy assay (<5 copies/ml) will be performed at the central virology laboratory on the stored plasma sample from the final visit in all patients who have VL <50 copies/ml on conventional testing at the final visit.

7.2.2 CD4+ count

CD4+ counts will be measured at the local site laboratory using the standard flow cytometry method used by the site. The site laboratory will be required to demonstrate satisfactory participation in a recognised quality control programme for CD4+ count testing.

7.2.3 Resistance testing

Drug resistance is the key component of the primary endpoint, and hence the detection of new resistance mutations needs to be pursued fastidiously in this trial.

All patients who have virological rebound more than 50 copies/ml on 2 consecutive readings (taken at least 4 weeks apart) will have a sample sent for genotypic resistance testing (from the sample that gave the highest VL result, or if there is less than 50 copies/ml difference in the VL results, the later of the two samples will be chosen in preference). Resistance testing will be performed by the local laboratory that is normally used by the site. A designated referral laboratory, normally used by the site for performing resistance testing at low VL levels, may be used also. In the event that sequencing is unsuccessful, the sample will also be tested by the study central resistance laboratory at UCL/UCLH. All the sequences will be analysed using the Stanford algorithm, and the level of resistance to individual drugs will be classified as none (susceptible), potential low level, bw level, intermediate level, high level.

Comparison will be made with the drug resistance profile obtained from any other previous sequences available for that patient (pre-treatment resistance testing is commonly performed at most centres in the UK, and prior resistance testing is mandated in the trial entry criteria for patients who have failed previous ART). If a patient develops virological rebound with resistance during the course of the trial but does not have a prior resistance test result for comparison, attempts will be made to identify a stored (pre-treatment) sample and if available this sample will be tested to determine whether transmitted resistance was present prior to antiretroviral therapy.

As a further measure to make the best possible comparison of the two treatment strategies in terms of drug resistance development, stored samples from patients who have rebounded (VL >50 copies/ml) will be tested using a minority species resistance assay at the central virology laboratory at the end of the trial.

7.2.4 Quality of Life (QoL) assessment

This will be assessed using the Medical Outcomes Study HIV Health Survey (MOS-HIV), a 30-item QoL questionnaire based on the SF36 which has been validated for use in patients with HIV infection (22) (see Appendix 6). The questionnaire takes about 5 minutes for patients to self-complete, and this will be done at baseline, at 12 weeks, and annually during the trial.

7.2.5 Neurocognitive assessment

Neurocognitive function will be assessed at Baseline, Week 12, annual visits and the final trial visit using a series of simple neuropsychological tests that can be administered by a clinician or research nurse without specific neuropsychological training, and that will take about 20 minutes to perform. The most common neurocognitive impairments seen in HIV-infected individuals are those that affect frontal sub-cortical functions (23-25). Therefore, the tests have been chosen to detect changes in these functions such as psychomotor speed, memory, executive functions (e.g. processing instructions) and fine motor speed. The following simple, well-established tests will be performed (details provided in Appendix 13):

- Hopkins Verbal Learning Test - Revised. This assesses verbal learning and memory. The examiner reads 12 words and the participant is asked to recall them immediately. The exercise is performed a further two times in exactly the same way. The free recall trials are followed by a recognition test where the examiner reads aloud a list of 24 words and the participant must answer yes or no for each of them depending if the word was or was not included in the original list of 12 words. Finally, after performing the remaining tests listed below and completing the MOS-HIV quality of life questionnaire (i.e. after about 15-20 minutes), the initial free recall test is repeated (without the examiner repeating the list again) to assess delayed memory. A final score based on the number of words recalled or recognised in each part of the test will be calculated (a separate score for immediate and for delayed memory will be produced).

- Trail making tests (two parts). These assess psychomotor speed and cognitive flexibility within the executive functioning domain (26). In Part A, participants will be asked to connect a series of encircled numbers in numerical order. In Part B they will be also asked to connect 25 encircled numbers and letters in numerical and alphabetical order in an alternating fashion. The score is the time to completion of each of the tasks.

- Grooved Pegboard test. This assesses psychomotor speed and fine motor function. It is a manipulative dexterity test consisting of 25 holes with randomly positioned slots. Pegs have a key along one side and they must be rotated to match the hole before they can be inserted. Participants are asked to insert the pegs into the slots as rapidly as possible, and the test will be performed with both the dominant and the non-dominant hand. The score is the time to completion of the task (each hand scored separately).

The participant will be given their raw test scores if so desired. The investigator will be provided with a table in which raw scores are categorised as average, above average, well above average based on standard population data so that some interpretation of the participant's score can be made, if the participant wishes results to be expressed in that way.

The final evaluation of each participant's neurocognitive function will be done centrally to calculate a neurocognitive function summary score, as described in section 9.5.2.

7.3 Procedures for assessing safety

A symptom evaluation and targeted physical examination will be performed at each visit.

Body composition changes will be evaluated at baseline and annual visits as follows:

- Waist circumference will be measured between the lower border of the ribs and the iliac crest, in a horizontal plane.

- Hip circumference will be measured at the widest point over the buttocks.

- Patients will be asked about any loss of fat in the face, and asked to say whether they consider that these changes are easily noticed by others (classified as severe). The physician will confirm on examination whether the patient has readily noticeable facial lipoatrophy (classified as severe).

Cardiovascular risk factors will be assessed at annual trial visits, and risk will be quantified using charts based on the Framingham equation (19) (see Appendix 11).

Blood will be drawn at trial visits to assess laboratory safety parameters according to standard-of-care as indicated in the schedule of trial assessments (see section 1.3). Additional safety blood tests or investigations will be performed to investigate symptoms or monitor emergent laboratory test abnormalities as clinically indicated.

All adverse events will be reported on the case report form. Adverse events (clinical and laboratory) will be graded using the 1992 Division of AIDS toxicity grading scale (see Appendix 7). Serious adverse events will be defined according to the EU Directive 2001/20/EC Article 2 based on ICH GCP, and will be reported to the MRC CTU according to standard timelines (see section 11).

Diagnostic criteria for selected serious AIDS and non-AIDS events are defined in the protocol (see section 9.2.2 and Appendices 8 and 9), and sites will be encouraged to investigate patients in a way that allows determination of whether patients meet the specified diagnostic criteria. An independent endpoint review committee will review these endpoints to ensure that they satisfy the criteria.

7.3.1 Procedures for Therapeutic Drug Monitoring

Patients in the PI monotherapy arm will have a blood sample taken at Week 4 (and possibly repeated at Week 8 or 12) for measurement of PI concentration. The sample should be a trough sample (i.e. taken at the time when the next dose of medication would ordinarily be due) if at all possible, or obtained at the very least 4 hours following the last dose. The time of the last dose of PI taken will be recorded.

Samples will be sent from sites using the normal procedures for dispatching samples for therapeutic drug monitoring which is performed in the UK by Delphic Diagnostics. Results will be made available to the sites within approximately 2 weeks of sample collection. When a trough sample was not available, population pharmacokinetic data will be used to predict the trough level. Advice on whether dose modification of the PI may be indicated will be provided with the result.

PI concentration will also be measured in patients who have a confirmed VL rebound, to assist with the interpretation of the causes of rebound. These samples may be stored for later testing in batches. The results will not be essential for clinical care because the patient will have switched back to triple-therapy. The results will be reported to the treating clinician but this may not be in real time.

7.4 Procedures for assessing health economics

The trial will measure all the costs (from an NHS perspective) of participants in the trial regardless of why costs were incurred, starting 3 months prior to randomisation and continuing for the duration of follow-up. Data on service receipt (resource utilisation) will be collected at each trial visit by asking patients about visits to HIV clinics or GPs, days off work due to illness, and any periods of hospitalisation since the previous trial visit (or during the 3 months prior to randomisation). The duration of hospitalisation and main diagnosis will be recorded (verified if possible by reference to a hospital discharge summary). Patients will complete the EQ-5D questionnaire (see Appendix 5) at each trial visit to permit cost-utility analysis (27).

7.5 Trial closure

All patients will be followed according to the trial schedule until a common trial closing date. The trial will be closed after all data queries have been resolved.

8. LOSS TO FOLLOW-UP & WITHDRAWAL

8.1 Patient transfers

For patients moving from the clinical site, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient. MRC CTU should be informed and a copy of the patient CRFs will need to be provided to the new site. The patient will have to sign a consent form at the new site, and until this occurs, the patient remains the responsibility of the original centre.

8.2 Loss to follow-up

A patient will be regarded as 'lost to follow-up' if they have not been seen in clinic for more than 8 months. After this time, a check will be performed through disease databases or death registers (e.g. Office for National Statistics, CDSC Colindale). Consent will be obtained for this when the patient enters the trial (see Appendix 2). Subsequently, if the patient attends clinic and a CRF is received by the MRC CTU, the 'lost to follow-up' status will be reversed.

8.3 Withdrawal of consent

In consenting to the trial, patients are consenting to treatment according to the allocated treatment strategy as well as to trial follow-up visits and data collection. If a patient wishes to withdraw from the trial treatment strategy, the doctor/nurse will explain the importance of remaining on trial follow-up or, failing this, of allowing routine clinic follow-up data to be used for trial purposes.

If the patient explicitly states their wish not to contribute further data to the trial, the trial doctor should inform the MRC CTU in writing (i.e. a withdrawal CRF should be completed). Data up to the point of withdrawal can be included in the analysis. Further data i.e. vtal status can only be obtained through NHS databases and registers (as above).

9. STATISTICAL CONSIDERATIONS

9.1 Method of randomisation

Patients will be randomised using a computer-generated algorithm based on random permuted blocks.

9.2 Outcome measures

Analyses will compare the PI monotherapy and standard treatment arms on the following outcome measures:

9.2.1 Primary outcome measure

- **Loss of future drug options**
  Defined as the first occurrence of intermediate to high level resistance to any one or more of the standard antiretroviral drugs (limited to licensed drugs in contemporary use) to which the patient's virus was considered to be sensitive at trial entry (i.e. excluding drug resistance that was known to be present on previous resistance testing).

9.2.2 Secondary outcome measures

- **Serious drug or disease-related complication**
  Defined as the first occurrence of one of the following in any individual patient:
    - **Death from any cause**
    - **Serious AIDS-defining illness** (see diagnostic criteria, Appendix 8)
    - **Serious non-AIDS defining illness** (see diagnostic criteria, Appendix 9)
        - Acute myocardial infarction
        - Coronary artery disease requiring invasive procedures
        - Cirrhosis
        - Acute liver failure
        - End-stage renal disease
        - Stroke
        - Clinical acute pancreatitis
        - Severe lactic acidaemia
        - Severe facial lipoatrophy
        - Severe peripheral neuropathy
        - Non-AIDS malignancy

- **Adverse events**
  Defined as the total number of Grade III and IV adverse events.

- **Virological rebound**
  Defined in two ways using the "Time to loss of virologic response" (TLOVR) algorithm (28):
    - Two consecutive tests, taken at least 4 weeks apart, with VL more than 50 copies/ml (the first test must also be confirmed by re-testing the same blood

sample). Patients who have virological rebound in the PI monotherapy arm, but re-suppress VL to <50 copies/ml with re-introduction of NRTIs, will not count as failures; OR

- As above, with at least one of the samples giving a VL result more than 400 copies/ml.

- **CD4+ count change**
  Defined as change from baseline in absolute CD4+ count.

- **Health-related Quality of Life change**
  Defined as change from baseline in the mental and physical health summary scores.

- **Neurocognitive function change**
  Defined as change from baseline in the neurocognitive function summary score.

- **Cardiovascular risk change**
  Defined as change from baseline in the risk of cardiovascular disease calculated from the Framingham equation (19).

- **Health care costs**
  Defined as the total cost of health care resources utilised per patient year.

9.2.3 Health economic analysis

A full health economic analysis will be conducted to determine the relative cost-effectiveness of the alternative management approaches.

9.3 Sample size

As the strategy of PI monotherapy is likely to offer a major advantage in terms of cost (approximately 50% cost reduction from standard-of-care) and possible advantages in terms of long-term tolerability compared to standard-of-care, the trial aims to demonstrate that PI monotherapy is non-inferior to the standard-of-care by a pre-defined amount in terms of the primary endpoint (non-inferiority trial).

The estimation of the sample size is based on the following assumptions using a time-to-event analysis (29):

1. 90% of patients on the standard-of-care arm will maintain all future drug options (i.e. remain free of new resistance mutations) over three years. This figure is based on an analysis of resistance development during subsequent follow-up for patients who have taken an established NNRTI-based regimen for at least 12 months in the UK CHIC study, following the methodology used by Phillips et al (30).

2. The PI monotherapy arm will be considered "non-inferior" if the upper limit of the 95% confidence interval (2-sided) for the difference in the proportion of patients who maintain all future drug options over three years (standard-of-care – PI monotherapy) is less than 10%. This is consistent with the majority of HIV non-inferiority trials that use a cut-off of 10-15% and with FDA guidelines which recommend a cut-off of 10-12% (28, 31).

3. 85% power to detect non-inferiority according to criterion 2.

4. Recruitment occurs at a uniform rate over 18-24 months.

5. Total trial duration of 60 months.

6. Cumulative loss to follow-up is approximately 10% by 5 years.

Under these assumptions a total of 388 patients (194 per arm) are required. We therefore plan to recruit a total of 400 patients to yield approximately 40 events.

9.4 Interim monitoring and analyses

An Independent Data Monitoring Committee (IDMC) will be established to monitor the trial. A charter for the IDMC will be developed prior to starting the trial. The IDMC will meet around the time of trial initiation to establish terms of reference, after the first 100 patients recruited have reached 12 months of follow-up and at yearly intervals thereafter. The IDMC will also review safety data at each meeting, and may make recommendations about the conduct of the trial should any safety concerns be identified.

9.5 Analysis plan

A full statistical analysis plan will be developed before the trial is analysed. It will be based on the following summary:

9.5.1 Primary analysis

The primary analysis will compare the two groups as allocated (intention to treat, ITT) in terms of loss of future drug options (see precise definition of primary outcome measure, above). Time-to-event methods (Kaplan-Meier plots and Cox proportional hazard regression) will be used for this comparison. Although non-inferiority trials often place especial emphasis on a per-protocol analysis, this is less relevant for a strategy trial (such as this) than for an explanatory trial comparing the therapeutic efficacy of two drugs. However, we will conduct a sensitivity analysis excluding patients who switch from their randomised allocation within 3 months where this is due to personal preference rather than any clinical indication. In both ITT and per-protocol analyses patients who have died or who are lost to follow-up will be censored at their last viral load measurement. If non-inferiority is demonstrated, an analysis for superiority of the PI monotherapy arm will be performed.

9.5.2 Secondary analyses

The primary analysis will be extended to tabulate individual ART drug options and ART class options which are lost due to the development of resistance. Time-to-event methods will be used to analyse the rate of serious drug- or disease-related complications and for viral load rebound. Also, the frequency of grade III and IV adverse events will be tabulated by body systems and randomised group and the groups will be compared using the X^2 test. Repeated measures analysis will be used to compare change in CD4+ cell count from baseline in the allocated strategies.

Patient responses on the MOS-HIV questionnaire will be converted to scores on 11 subscales, ranging from 0 to 100, with higher scores indicating better health (32). The scores are then synthesised into a physical health summary score (PHS) and a mental health summary score (MHS). A general linear mixed model will be used to compare the two groups in terms of changes from baseline in the summary PHS and MHS quality of life indexes over the follow-up period.

The scores on each of the neurocognitive tests will be standardised using demographic-adjusted normative means. This procedure will adjust the data for gender, age, level of

education and ethnic background. Briefly, standard scores will be calculated by subtracting the appropriate normative mean from the raw score and then dividing by the appropriate normative standard deviation to give a z score (33). The patient's individual z scores on each test will be averaged to give the patient's neurocognitive function summary score at each visit. A general linear mixed model will be used to compare the two groups in terms of changes from baseline in the neurocognitive function summary score.

Changes from baseline in the 10-year cardiovascular risk score will also be compared between the two groups using a general linear mixed model.

Economic analysis

An economic evaluation will be conducted from the health services perspective. Costs will cover the use of medication and laboratory tests as well as hospital, primary care and community health services. Unit costs will be attached to resource use, using the best available estimates of long run marginal opportunity cost, to obtain a cost per patient over the period of follow-up. Routinely available national unit costs will be used where possible (e.g. NHS Reference Costs, UK DoH 2005), with local estimations where necessary.

For the within-trial analysis, the differential cost of the treatment interventions will be related to their differential outcomes in terms of the primary outcome. The relative cost-effectiveness of the alternative forms of management will then be assessed using standard decision rules (34) and a full stochastic analysis will be undertaken. A cost-utility analysis will also be conducted based on EQ-5D health states. For each state, a utility is assigned as an adjustment factor for quality of life. Utility weights range from 0 to 1 where 0 represents death and 1 signifies perfect health. The total utility of a particular state is made up of the length of time spent in a state multiplied by the utility of that state. This will offer a simpler decision rule and allow explorations of cost per quality-adjusted life-year gained (QALY) (35). A cost consequence analysis will estimate, by randomised group, mean cost per patient and changes in EQ-5D 'utility'. Regression modelling will be used to explore variation in costs and utilities according to patient characteristics and by location of treatment (36) (37).

The within-trial analysis will be augmented by extrapolation beyond the trial follow-up using decision-analytic modelling (38). The aim of this analysis will be to predict the implications of any difference in clinical endpoints (in terms of drug therapy options, VL and viral sequencing for resistance mutations) in the trial for subsequent quality-adjusted survival duration and long-term resource costs. This will inform the question of whether any short-term savings in drug costs within the trial period are offset by additional costs or health decrements in the long-term. The model will probably take the form of a state transition model and is likely to be based on a model currently in development as part of the OPTIMA (www.optimatrial.org/uk) trial. The ultimate outputs of the economic evaluation will be estimates, by treatment group, of long-term quality-adjusted survival duration and costs including the presentation of incremental cost per quality adjusted life year as necessary. In addition, probabilistic methods will be used to present the probability that the two forms of management are cost-effective in the long-term. Scenario analysis will be used to explore the range of structural assumptions used in the analysis.

10. TRIAL MONITORING

10.1 Risk assessment

The trial will use only licensed drugs, and the risks and management of drug-related toxicities are known. The trial is classified as low risk and the monitoring plan has been designed accordingly.

10.2 Monitoring at MRC CTU

Data stored at MRC CTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. If any such problems are identified, the site will be contacted and asked to verify or correct the entry. Any data which are changed should be crossed through with a single line and initialled. Changes should be made on the original CRF and a copy of the amended page(s) will be sent to the MRC CTU by fax or post. MRC CTU will send reminders for any overdue and/or missing data.

10.3 Clinical site monitoring

On-site monitoring will be conducted at all sites at a frequency of at least one visit per year. The first monitoring visit for each site will be performed after 4-6 patients have been enrolled or at 6 months following the date the site received approval to enrol patients, whichever occurs first. The CRFs of all patients enrolled will be reviewed at the first monitoring visit. For high-recruiting sites, a sample of no less than 5 patients will be selected by the MRC CTU for review at subsequent visits. Priority will be given to selecting patients for whom the CRFs have not been previously monitored.

MRC monitors will:

- verify completeness of Trial Master File
- confirm adherence to protocol
- review eligibility verification and consent procedures
- look for missed event reporting
- verify completeness, consistency and accuracy of data being entered on CRFs
- provide additional training as needed

The monitors will require access to all patient medical records including, but not limited to, laboratory test results and prescriptions. The investigator (or delegated deputy) should work with the monitor to ensure that any problems detected are resolved.

10.4 Data quality assurance

Data will be entered into the trial database at the MRC CTU from a copy of the CRF faxed or sent from the site. The site will retain the original CRF. Where possible de-identified laboratory reports (labelled with patient trial identification number) will be faxed to the MRC

CTU. All data recorded in each CRF will be entered on to the trial database, and then printed reports directly obtained from the database will be checked by different data-entry personnel.

10.5 Confidentiality of trial documents and patient records

The investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorised parties. Patients will be assigned a trial identification number and this will be used on CRFs, patients will not be identified by their name. The investigator will keep securely a patient trial register showing identification numbers, names and date of birth.

11. SAFETY REPORTING

ICH GCP requires that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol. Section 11.1 lists definitions, section 11.2 gives details of the institution/investigator responsibilities and section 11.3 provides information on MRC CTU responsibilities.

11.1 Definitions

The definitions of the EU Directive 2001/20/EC Article 2 based on ICH GCP apply in this trial protocol. These definitions are given in Table 1.

Table 1: Safety Reporting Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (or Investigator Brochure) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: • result s in death • is life-threatening* • requires hospitalisation or prolongation of existing hospitalisation** • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect

11.1.1 Clarifications and Exceptions

*The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

11.2 Institution/Investigator responsibilities

11.2.1 Investigator Assessment

(a) Seriousness
When an AE/AR occurs, the investigator responsible for the care of the patient must first assess whether the event is serious using the definition given in Table 1.

(b) Causality
The Investigator must assess the causality of all serious events/reactions in relation to the trial therapy using the definitions in Table 2. There are 5 categories: unrelated, unlikely, possible, probable and definitely related. If the causality assessment is unrelated or unlikely to be related the event is classified as a SAE. If the causality is assessed as either possible, probable or definitely related then the event is classified as a SAR.

Table 2: Definitions of causality

Relationship	Description	Event Type
Unrelated	There is no evidence of any causal relationship	SAE
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).	SAE
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

(c) Expectedness
If the event is a SAR the Investigator must assess the expectedness of the event. The definition of an unexpected adverse reaction (UAR) is given in Table 1. If a SAR is assessed as being unexpected it becomes a SUSAR.

(d) Notification
Please also refer to the safety reporting flowchart on the following page
All AEs/ARs, whether expected or not, should be graded using the toxicity table in Appendix 7 and should be then recorded in the toxicity (symptoms) section of the appropriate visit CRF. This should be sent to the MRC CTU within one month of the form being due.

All non-treatment-related SAEs and all expected treatment-related SAEs (SARs) are *exempted* from expedited reporting i.e. only SUSARs require expedited reporting. (Adverse drug reactions to licensed PIs will continue to be reported by the investigator to the The Yellow Card Scheme run by the MHRA and Commission on Human Medicines).

All SAEs/SARs, whether expected or not, should be graded using the toxicity table in Appendix 7 and should be then recorded on an Event CRF. Investigators should record all

SAEs occurring from the time of randomisation until 30 days after the last protocol treatment administration.

A Safety Reporting Flowchart (Figure 2) is given at the end of this section to help explain the classification and reporting of events. Any questions concerning this process should be directed to the MRC CTU in the first instance. The notification procedure is as follows:

1. The Event CRF must be completed by the investigator (clinician named on the Delegation of Authority log who is responsible for the patient's care), with due care being paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible investigator, the form should be completed and signed by a member of the site trial team. The responsible investigator should subsequently check the Event CRF, make changes as appropriate, sign and then re-fax to the MRC CTU as soon as possible. The initial report shall be followed by detailed, written reports as appropriate.

2. Send the Event CRF by fax to the MRC CTU, fax number: + 44 (0)20 7670 4817.

3. Follow-up: Patients must be followed-up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. Follow-up information should be noted on a further Event CRF by ticking the box marked 'follow-up' and faxing to the MRC CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The patient must be identified by trial number, date of birth and initials only. The patient's name should not be used on any correspondence.

4. Staff at the institution must notify their local research ethics committee (LREC) of a SUSAR event (as per the institution's standard local procedure).

11.3 MRC CTU responsibilities

Medically qualified staff at the MRC CTU will review all event reports received. The causality assessment given by the local investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided in any subsequent reports.

The MRC CTU is undertaking the duties of trial sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authority (MHRA) and the research ethics committees according to standard procedures and within standard timelines.

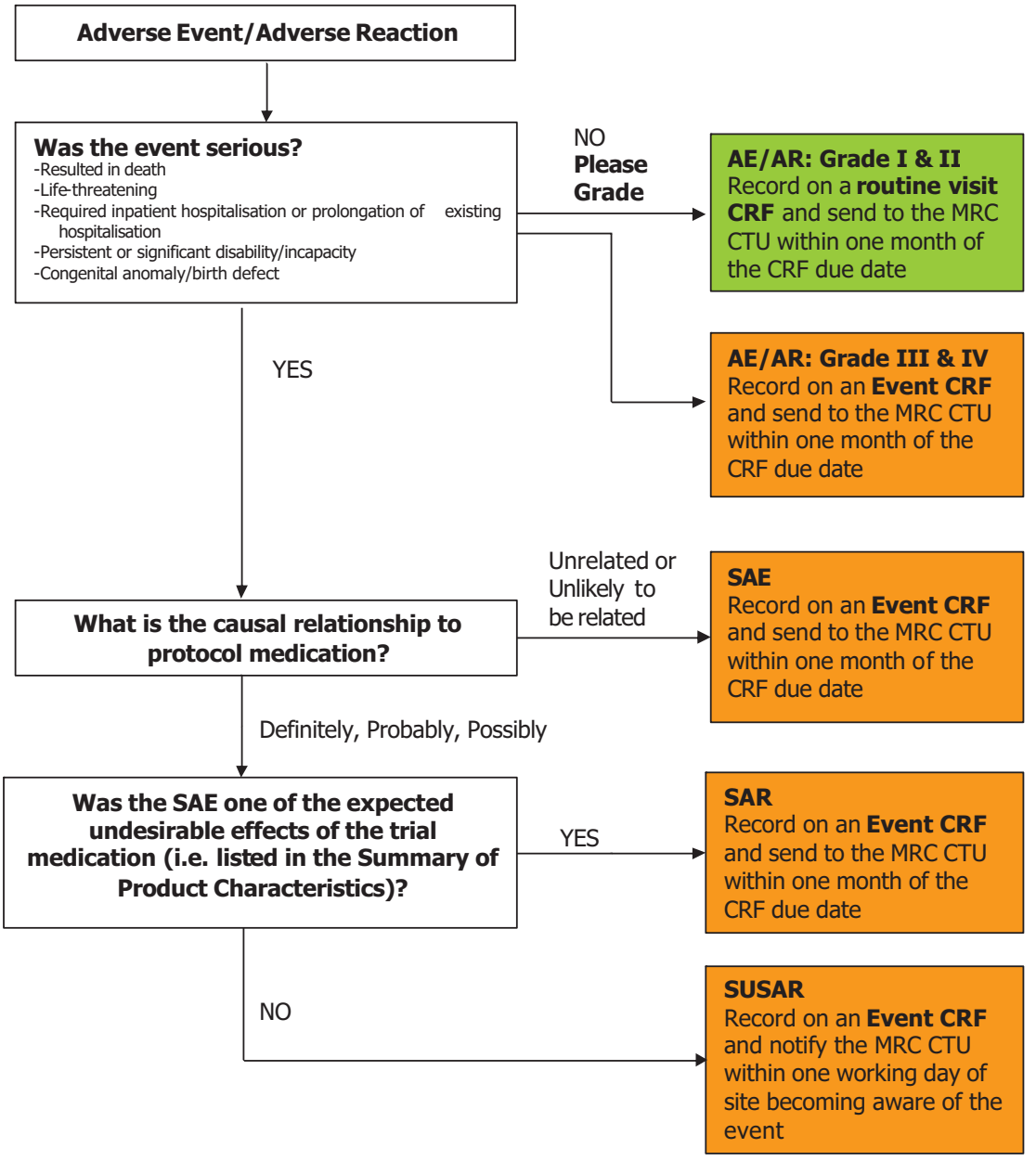
The MRC CTU will keep all investigators informed of any safety issues that arise during the course of the trial. Every 6 months the CTU will write to the investigators listing all SUSARs, providing information on the event, date of occurrence and body system. In addition, upon request of the TSC, the MRC CTU will inform investigators of any safety issues identified by the IDMC in their report(s) to the TSC.

SUSAR NOTIFICATION

Within one working day of becoming aware of an SUSAR, please fax a completed Event CRF to the MRC Clinical Trials Unit on:

Fax: +44 (0)20 7670 4817

Figure 2: Safety Reporting Flowchart



CRF: Case Report Form
SAE: Serious Adverse Event
SmPC: Summary of Product Characteristics
IB: Investigator's Brochure
SAR: Serious Adverse Reaction
SUSAR: Suspected Unexpected Serious Adverse Reaction

12. ETHICAL CONSIDERATIONS & APPROVAL

12.1 Ethical considerations

12.1.1 Risks and benefits to trial participants

See section 2.3 for detailed discussion of risks and benefits of the PI monotherapy strategy used in this trial. The risks include the risk of side effects arising from the change in medication, which are known and quantifiable since the trial will only use licensed drugs.

There is a very small increased risk of cardiovascular disease that may be partially abrogated by medication to treat hypercholesterolaemia, a potential increased risk of virological failure with the development of drug resistance, and the potential risk of virological rebound in the genital compartment with the theoretical increased risk of HIV transmission to others. These risks are all very small.

The benefits may be a potential reduced risk of long-term toxicity resulting from withdrawal of other medications, and the potential reduced risk of virological failure and drug resistance thereby leading to better preservation of future drug options. The trial may benefit society by finding an alternative long-term HIV disease management option.

12.1.2 Burden of investigations

The trial will use only licensed drugs, and the risk and management of drug-related toxicities are known. There is no placebo used. The protocol allows for switches within strategy. Apart from 2 extra monitoring blood tests in the first 6 months after enrolment in the PI monotherapy arm, the remainder of the trial visits coincide with the usual frequency of visits for routine clinical care, and the amount of extra blood taken is modest. Hence there are no ethical issues with the burden of investigations.

12.1.3 Informing potential trial participants of possible benefits and known risks

Participants will be informed fully of known risks and possible benefits by means of a patient information sheet and this will be reinforced by discussions with the trial research teams at the individual sites prior to enrollment.

12.1.4 Confidentiality

Patients' confidentiality will be maintained throughout the trial. Data submitted to MRC CTU and samples sent to central testing facilities will be identified only by the trial number and patient initials.

12.2 Ethical approval

The protocol will be submitted for ethical approval to an independent research ethics committee (REC) in the UK and for Site Specific Assessment at each of the participating sites. A copy of local R&D approval and the Patient Information Sheet and Consent Form on local-headed paper should be forwarded to the MRC CTU before the first patient is enrolled at site.

Each patient's consent to participate in the trial will be obtained after a full explanation has been given of the treatment options. The right of the patient to refuse to participate in the trial without giving reasons must be respected.

After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient

will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the patient must remain free to withdraw from the trial medicine or trial follow-up, at any time, without giving reasons and without prejudicing his/her further treatment.

13. REGULATORY ISSUES

This trial will be reviewed by an independent research ethics committee (REC) in the UK. The trial will be registered with the Competent Authority, the Medicines and Healthcare products Regulatory Agency (MHRA) UK.

This trial has been granted a UK Clinical Trial Authorisation (CTA), reference 2007-006448-23.

Investigators may not enrol patients into this trial until:

- The necessary notification or approval of the protocol and any amendments has been given by the MHRA.
- The approval of the protocol and any amendments has been given by the REC.
- The approval of the institution's local ethics committee and R&D has been obtained.

During the course of the trial the MHRA or REC may request review of trial and data on patients involved in the trial.

14. INDEMNITY

The MRC is the sponsor of the trial. The MRC and NHS are both publicly funded bodies and are not allowed to purchase advance insurance to cover indemnity because they are backed by the resources of the Treasury.

14.1 Liability

14.1.1 Circumstances where MRC will accept liability

The MRC is willing to accept liability in cases where:

(i) it sponsors the research: namely where it takes responsibility for initiating, managing and having day-to-day oversight of the research in question (including any research carried out by its Units); and

(ii) the MRC, or any of its employees, or any person formally acting with Council's authority, have been negligent or have failed to adhere to the relevant guidelines/guidance, legislation or procedure on good practice in relation to medical research; and

(iii) that negligence or failure to adhere to legislation, etc has caused or has materially contributed to the harm suffered by the individual making the claim.

Except in cases where a no-fault compensation scheme has been established with respect to a specified clinical trial, where there has been no negligence and no lapse in procedures or adherence to relevant legislation or accepted best practice on the part of the MRC, the MRC will not accept legal liability for any injury or harm suffered by a participant of a research project (in other words the MRC will not accept that the MRC is legally required to make any payment in respect of any injury or death arising from a research project). In such circumstances, the MRC will, on a voluntary basis, be prepared to consider making an *ex gratia* payment to any individual who suffers harm as a result of being involved in the research, but only if:

(iv) the MRC is the sponsor of the research (as in 14.1.1 (i) above); and

(v) where the MRC is a joint sponsor of the research, the harm has not occurred due to the negligence or other fault of the other sponsor(s) - in such cases the MRC would expect that the other sponsor would provide indemnity.

Requests for compensation or *ex gratia* payments in such circumstances will be considered on a case-by-case basis in relation to the MRC policy on such payments.

14.1.2 Circumstances where MRC will not accept liability

Where medical research is carried out in a care organisation, whether the NHS or another organisation, that care organisation will continue to owe the same duty of care to patients who are also participants in research that it owes to any other patients. This duty is not affected by patients agreeing to participate in such research or the fact that the MRC may be the sponsor of such research. Care organisations (and not the MRC) continue to be responsible for any breaches of that duty of care with respect to participants of research. Similarly, responsibility for the quality of investigational products (e.g. investigational medicinal products, investigational devices) lies with the manufacturer of the product.

If the patient is harmed as a result of negligence of NHS staff while participating in this trial, then they may be able to seek compensation. In this situation indemnity is provided by NHS indemnity schemes and professional indemnity schemes.

15. FINANCE

The trial is funded by the NIHR Health Technology Assessment Programme. The HTA programme is part of the National Institute for Health Research. It produces independent research information about the effectiveness, costs and broader impact of healthcare treatments and tests for those who plan, provide or receive care in the NHS.

The trial will be coordinated by the MRC CTU. A written agreement with the site Principal Investigator and/or the Investigator's institution and the MRC CTU will outline the funding arrangements to sites.

16. TRIAL COMMITTEES

16.1 Trial Management Group

A trial management group (TMG) that will include the MRC CTU trial physician and/or chief investigator, the trial statistician, the MRC trial manager and data manager will be formed to conduct the day-to-day management of the trial. A charter will be developed to describe the functioning of the TMG.

16.2 Trial Steering Committee

A Trial Steering Committee (TSC) will be formed to provide overall supervision for the trial. This will include an independent Chairman, two other independent clinicians, a community representative, the Chief Investigator, external clinical principal investigator and the trial statistician. A charter will be developed to describe the functioning of the TSC.

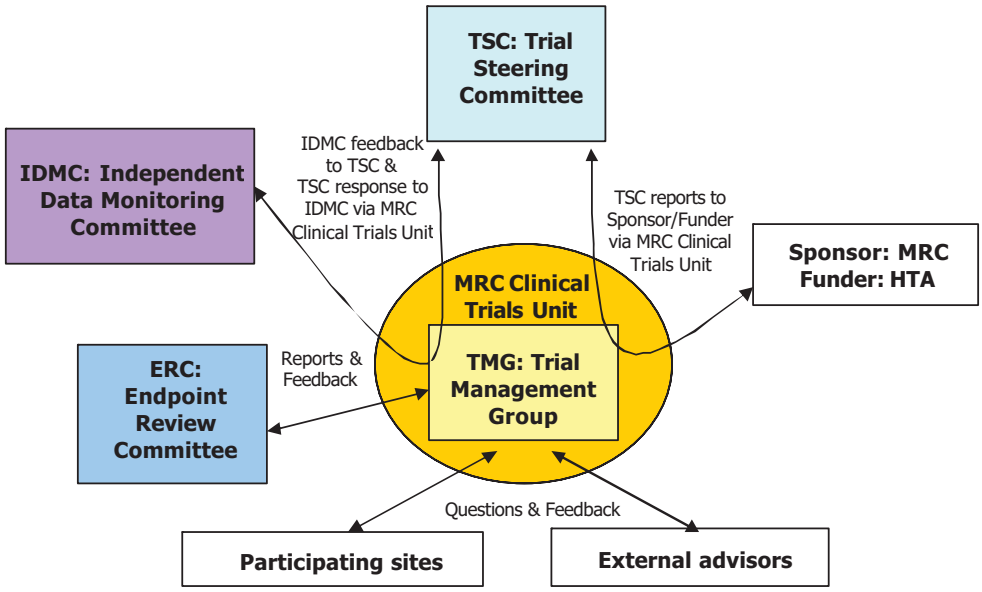
16.3 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be formed comprising two clinicians, a community representative, and a statistician, none of whom have direct involvement with the trial. The IDMC will report to the TSC. A charter will be developed to describe the functioning of the IDMC.

16.4 Endpoint Review Committee

An Endpoint Review Committee (ERC) will be formed to review the documentation relating to reported serious drug or disease-related clinical events, in order to ascertain whether these meet the criteria for this secondary endpoint. The ERC will consist of two clinicians, one of whom will not be directly involved with the trial.

Figure 3: Diagram of relationships between trial committees



17. PUBLICATION

It is anticipated that a number of opportunities will arise for publication during the course of, and following completion of this trial. In order to avoid disputes regarding authorship, it is important to establish a consensus approach that will provide a framework for all publications derived in full or in part from this clinical trial. The following approach is derived from the Lancet and from the publication policies used in OPTIMA and ESPRIT studies:

- All publications are to be approved by the TMG and TSC before submission for publication. The TMG and TSC will resolve problems of authorship and maintain the quality of publications.

- Trial findings will be submitted to journal(s) that support open access publication within the time frame specified by the MRC policy. All publications will acknowledge the HTA and any other appropriate funding sources.

- For all publications, the TSC will either nominate a chairperson or approve an individual's request to chair a manuscript writing committee. The chair will usually be the primary or senior author. The chairperson is responsible for identifying fellow authors and for determining with that group the order of authorship that will appear on the manuscript. The proposed writing committee will be submitted to the TSC for ratification prior to the first draft of the manuscript.

- The chairperson of any writing committee will also provide the TSC with a list of investigators to be presented in an appendix at the end of the paper. This list will include investigators who contributed to the investigation being reported but who are not members of the writing committee. In principle, sub-study reports should include all investigators for the main study, although in some instances where a smaller number of investigators have made any form of contribution, it may be appropriate to abbreviate the listing. All headline authors in any publication arising from the main study or sub-studies must have a made a significant academic/project management contribution to the work that is being presented. "Significant" must be defined by a written declaration of exactly what the contribution of any individual is believed to have been. In addition to fulfilling the criteria based on contribution, additional features that will be considered in selecting an authorship group will include the recruitment of patients who contributed data to any set of analyses contained in the manuscript, and /or the conduct of analyses (laboratory and statistical), leadership and coordination of the project in the absence of a clear academic contribution.

- The data derived from this clinical trial are considered the property of the MRC. The presentation or publication of any data collected by the participating investigators on patients entered into this trial is under the direct control of the TMG and TSC. This is true whether the publication or presentation is concerned directly with the results of the trial or is associated with the trial in some other way. However, although individual participating investigators will not have any inherent right to perform analyses or interpretations or to make public presentations or seek publication of any of the data other than under the auspices of and with the approval of the TMG and TSC, they will be encouraged to develop sub-studies or propose analyses subject to the approval by the TMG and TSC.

- Outcome data by treatment group will not be revealed to the participating investigators until the data collection phase of the trial has been completed. This policy safeguards against possible bias affecting the data collection. The IDMC will be monitoring the outcome results and may recommend that the trial be stopped for safety reasons or if a definitive answer is reached earlier than the scheduled end of the trial.

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APPENDICES

APPENDIX 1: PATIENT INFORMATION SHEET

[To be presented on local-headed paper]

Patient Information Sheet – Part 1

Version 1.1, 25 March 2008

1. Study title

PIVOT: Protease Inhibitor monotherapy Versus Ongoing Triple-therapy in long-term management of HIV disease

EUDRACT: 2007-006448-23
ISRCTN04857074

2. Invitation

You are being invited to take part in a research study. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

- Part 1 tells you the purpose of this study and what will happen to you if you take part.
- Part 2 gives you more detailed information about how the study will be carried out.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

3. What is the purpose of the study?

Currently, we use a combination of three drugs to treat HIV. These drugs are called anti-retroviral treatment or ART. The drugs that usually make up ART are:

- two nucleoside reverse transcriptase inhibitors (NRTIs)
- one non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI)

These drugs seem to be very effective and do not cause many side effects in the short-term, but they do need to be taken life-long and may be associated with side effects after many years. It is possible that there are alternatives to triple therapy that are just as effective and have less long-term side effects. It is also possible that there are alternatives that, in the long run, will be less susceptible to develop drug resistance and so will preserve more treatment choices for the future.

One possible long-term treatment option is to simplify treatment to just one drug, a PI, instead of the standard triple therapy. There is some evidence from previous clinical trials that patients who are stable on triple-therapy can simplify their treatment to PI monotherapy (one drug) and successfully maintain undetectable viral load as well as experience less side effects when they stop their NRTIs.

The purpose of this study is to find out whether a strategy of trying PI monotherapy, with the plan of switching back to triple therapy if viral load control is not adequate, is just as good as continuing standard triple-therapy in long-term treatment of HIV disease.

4. Why have I been chosen?

You have been chosen for this study because you are taking standard combination ART, described above, and you have had an undetectable viral load for at least the last 6 months. Overall 400 patients like you will take part in the study.

5. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard-of-care you receive.

6. What will happen to me if I take part?

Study screening and entry

Before you join the study, we will need to review your medical history and do some tests to make sure you are suitable. You will need to come to the clinic in the morning with an empty stomach (nothing to eat or drink from midnight before the visit, other than water and your medication) so that we can measure your cholesterol and glucose as well as some other routine blood tests. We will also need to perform an ECG (an electrical recording of your heart). Some of these tests may not need to be repeated if you have had them done in the previous 6 months. If these tests do not show any major abnormalities and you meet all the criteria for the study, then will be able to participate in the study.

Study treatment

The study is a randomised controlled clinical trial. This means that once you have agreed to enter the trial, you will be allocated by chance to either the standard triple-therapy group or the PI monotherapy group. Everyone has an equal chance of being in either group. Allocating treatment this way means that the groups of people getting each treatment should be similar, so that if there are any differences between how the groups do we know it will be due to the treatment allocation.

If you are allocated to the standard treatment group, you will carry on with your current treatment and continue to have regular monitoring as described in the next paragraph. You will be able to change your therapy in the future if there is a good clinical reason to do so (for example, if you develop viral load rebound or side-effects from the drugs), but if you change therapy it should be according to current guidelines (i.e. should consist of at least 3 drugs which are effective against HIV).

If you are allocated to the PI monotherapy group, you will stop all your current ART drugs that are not PIs, and will start or continue on just a boosted PI (boosted means it is given with a small dose of ritonavir, another PI, to increase the level of the main PI and to allow less frequent dosing). There are several PIs that may be considered for use as monotherapy, and the choice of which PI to take will be left up to you and your clinic doctor to decide. Your clinic doctor will be able to advise you on the relative merits of the different PIs, as they may differ in terms of the dose frequency, potential side effects, and possibly in effectiveness. You will be able to change to an alternative PI as monotherapy during the study if you develop any side-effects or if there are other reasons why you, or your doctor, believe that an alternative PI might be better for you. You will be expected to continue treatment with PI monotherapy until the end of the study, but you will be able to return to standard triple therapy if there is a good clinical reason to do so (for example you develop viral load rebound, or you develop side effects from the PI that you are on that cannot be controlled satisfactorily with additional medication or by switching to an alternative PI). If you do need to return to taking standard triple-therapy that will usually be the same combination that you were taking when you entered the study. During the study you will continue to have regular monitoring as described in the next section.

Study assessments and follow-up

You will be involved in the study for about 3 to 5 years (depends on how long the study has already been running when you join), during which time you will need to visit the clinic on a regular basis to check how you are doing. However, the clinic visits are at approximately the same frequency that you would be coming to the clinic anyway for routine care, even if you were not taking part in the study. The visits will be at Day 0 (the day you enter the study and that you change to PI monotherapy, if allocated to that option) and then approximately every 12 weeks up to the end of the study.

At each of these routine visits the research nurse and/or your doctor will ask you a few questions about your medication and whether you have any symptoms, and may perform a brief examination. They will ask you to complete a checklist of your health status (takes less than 1 minute to do) and will draw some blood for routine blood tests (viral load, CD4 count, full blood count, kidney and liver function tests). These routine visits (which account for most of the visits in the study) are very similar to what you would have done anyway as part of your normal care.

At the week 12 visit, the annual study visits (every 48 weeks) and the last study visit, you will need to come in the morning with an empty stomach (nothing to eat or drink from midnight before the visit, other than water and your medication) so that we can also measure the level of cholesterol and glucose in your blood. We will also take an extra tube of blood at this visit to store in case future tests are needed. In addition to the assessments done at the routine visits, we will also do some neurocognitive (brain function) tests that involve testing your memory and reaction times, and ask you to fill in a quality of life questionnaire. These simple tests will take about 15 minutes in total.

If you are allocated to the PI monotherapy group, you will also need to come for two extra visits, at 4 weeks and 8 weeks after you start on your new treatment. For the week 4 visit, you will need to come in the morning with an empty stomach (nothing to eat or drink from midnight before the visit, other than water and your non-ART medication) and postpone your morning dose of PI medication until after the blood has been drawn. At this visit the research nurse or doctor will review how you are getting on with the new treatment, and will draw some blood for routine tests (including viral load, full blood count, kidney and liver function, cholesterol and glucose) and to measure the concentration of the PI in your blood. We will also take 1 extra tube of blood for storage in case of the need for future tests. At the week 8 visit, you will just have a blood sample taken for measurement of viral load (and possibly to check the PI concentration again, if the levels were low on the first test).

The total amount of blood needed for these routine tests will be about 40ml at screening, (8 teaspoons), 25ml (5 teaspoons) at day 0 and for most of the routine 12 weekly visits, and 35ml (7 teaspoons) at the week 12, annual and final study visits. For the week 4 and week 8 visits for those in the PI monotherapy group only, the amount of blood needed will be about 35ml (7 teaspoons) and 10ml (2 teaspoons) respectively. Almost all these blood samples would need to be drawn anyway for your routine care and the total amount of additional blood taken for specific research-related tests will average no more than 15ml (3 teaspoons) per year during the study.

In addition to these routine visits, if you have a rebound of viral load while you are in the study you will be recalled for a repeat viral load test at between 4 to 6 weeks from the date of the previous test. If this test confirms a rebound of viral load your clinic doctor will discuss with you the need to change your treatment. If you are in the PI monotherapy arm, this will mean restarting triple-therapy. If you have viral load rebound, the sample will also be sent for a resistance test, the results of which may guide you and your doctor as to the best choice of medication for you. At the end of the study all samples with viral load rebound will

be tested again using a very sensitive resistance test at a central laboratory to give the best information possible on resistance. All these results will be provided to your doctor.

You will not be paid to take part in the study, but your clinic may be able to reimburse reasonable travel expenses.

7. What do I have to do?

There are no particular lifestyle or dietary restrictions required for participating in this study, other than those associated with taking your medication each day. You will be expected to adhere to your study medication according to your allocated treatment group for the duration of the study, and to come for the clinic visits according to the study schedule. You will need to tell your doctor before you take any other medication or herbal treatments as some of these may interact with the PI or your other HIV medications.

8. What are the alternatives for treatment?

The alternative for treatment, if you don't participate in this trial, is to simply carry on with your usual combination HIV therapy, or to switch to other alternative treatments based on combinations of currently-licensed ART drugs. If you are experiencing unpleasant side effects from your current therapy then you should discuss with your doctor about switching to an alternative triple-therapy for at least 3 months before entering this trial. You should not enter the study if the side effects of your current therapy are so bad that they mean you would not be prepared to continue the treatment you are currently on for the duration of the study (which will be at least 3 years) if you were allocated to the combination therapy group.

9. What are the side-effects of any treatment received when taking part?

Both standard therapy and PI monotherapy may cause side effects during the course of this study. The side effects of PIs vary according to the particular drug taken, but the PIs that are most often prescribed now are generally well tolerated. The commonest side effects are gastrointestinal intolerance (such as diarrhoea or nausea), metabolic disturbances (such as high cholesterol and high blood sugar) and increased bilirubin level (which is harmless, but produces a yellow discoloration in the eyes). These side effects are mainly associated with particular drug(s), and can usually be managed by taking additional medication (e.g. to lower cholesterol) or by switching to an alternative PI. Your doctor will discuss with you the possible side effects of the PI that you choose to use, and will advise you on the appropriate management of any side-effects.

If you do develop any symptoms you should report them to your doctor. If you experience any serious side effects you should contact a member of the study team according to the contact details given on the emergency contact card.

10. What are the possible disadvantages and risks of taking part?

Possible risks and discomforts include the development of local bruising and discomfort where needles are inserted into a vein to collect blood, although you would be having blood taken as part of your routine care with approximately the same frequency even if you were not participating in this study.

If you are not taking a boosted PI-containing combination when you enter the study, there is a risk that you will develop new side effects if you are allocated to the PI monotherapy group and need to start a boosted PI. However, these side effects (outlined in question 9) can usually be controlled with changes in dose, switch to an alternative PI medication, or use of additional medication (e.g. to reduce cholesterol).

We expect that a small proportion of patients will experience low level viral load rebound when they switch to PI monotherapy (likely no more than 5-10%). Those who do rebound will need to switch promptly back to triple-therapy. It is almost certain, based on scientific

knowledge and results from other studies, that reintroduction of combination therapy will be successful in suppressing viral load to undetectable levels again. The risk of developing clinical resistance to the PI during this short time with a low level of viral load is very small. Overall, the risk of developing drug resistance appears to be no greater with PI monotherapy treatment than it is with triple-therapy. If you do develop resistance during the study, there are likely to be several other options available to you for treatment that have a high chance of success, and your clinic doctor will discuss these with you.

If you are taking PI monotherapy there is a theoretical risk of developing viral rebound and drug resistance in parts of the body where PIs do not achieve high levels (such as the brain and genital tract), even though the treatment is working well in suppressing viral replication in your blood. There is no evidence to date that this is associated with any adverse clinical consequences for you. If you have detectable viral load in genital secretions, there is a theoretically increased risk that you might transmit HIV to someone else if you do not practise safe sex. You should consider this risk to others carefully and we suggest that you discuss this with any regular sexual partner(s) before deciding whether or not to participate in this study .

If you are a woman who is pregnant, you should not enter this study. This is because current guidelines recommend that pregnant women should take combination therapy (PI monotherapy has not been tested) to prevent transmission to their unborn child. Although pregnant women have taken PIs in the past without harming the baby, it is possible that taking a PI during pregnancy may harm the unborn child. If you find that you have become pregnant while taking part in the study, you should immediately tell your study doctor. Any necessary changes to your ART combination during the pregnancy are permitted in this study.

If you have private medical insurance you should check with the company before agreeing to take part in the trial to ensure that your participation will not affect your medical insurance. In this situation you also need to consider whether disclosure of your HIV status may also affect your insurance.

11. What are the possible benefits of taking part?

If you take part and are allocated to the PI monotherapy group, you may have a reduced risk of long-term side effects by stopping the drugs you were taking as part of your triple combination therapy. The long-term side effects that you may be spared depend on the particular drugs that you stopped. They may include things like kidney damage, liver damage, nerve damage, loss of fat in the face, arms and legs and other long-term unwanted side-effects, both known and unknown, associated with NRTIs; metabolic disturbances (e.g. high cholesterol) and chronic neuropsychiatric problems (e.g. sleep disturbance, memory loss, poor concentration) associated with NNRTIs (especially efavirenz).

There is also a possibility that you may have less drug resistance and maintain more future long-term treatment options at the end of the study if you take PI monotherapy (because PI drugs are generally less prone to develop resistance).

You may also appreciate or benefit from some of the extra testing that is done as part of this study, for example the neurocognitive tests, the PI drug level testing (in the PI monotherapy group), the more detailed drug resistance testing as well as the extra attention to details of your care that is associated with participation in a clinical trial.

If you take part in this study, you'll be helping us to learn more about the best ways to treat people with HIV. Having people like you join a randomised controlled trial is the only way that we can find out for sure whether PI monotherapy is as good as (or perhaps better than) conventional combination treatment for the long-term management of HIV disease. If the

study does show that PI monotherapy is at least as good as conventional treatment then this will be an important finding. It will increase the number of treatment options available for long-term management of HIV disease and this may be of benefit to you and other people like you in the future. PI monotherapy is more economical than triple-therapy, so if it works as well as triple-therapy, we'll be able to free up healthcare resources that could be used to improve other aspects of HIV care.

12. What happens when the research study stops?

When the study ends, you will still be able to continue to access medication and continue to be monitored as part of routine clinical care. If you are doing well on PI monotherapy you could continue this if you and your doctor wish to do so, or switch back to combination triple-therapy while you wait to hear about the results from the trial. If you are on combination therapy, it would be sensible to continue this while you wait for the results of the trial. When the results of the trial are available your doctor will talk with you about which option would be the best for you in the long-term.

13. What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed individually. Detailed information on this is given in Part 2 of the information sheet.

14. Will my taking part in this study be kept confidential?

Yes, all the information about your participation in this study will be kept confidential. The details are included in Part 2.

15. Contact for Further Information

If you have any further questions about this study please discuss them with your doctor. You may also find it helpful to contact the i-Base Treatment Information phone line: 0808 800 6013 (open Mon-Wed 12-4pm), or website: www.i-base.org.uk

If you would like further information on this study please ask:

..... who can be contacted at .....

or .....at ..... who is the local principal investigator.

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

[To be presented on local-headed paper]

Patient Information Sheet – Part 2

Version 1.1, 25 March 2008

1. Study title

PIVOT: Protease Inhibitor monotherapy Versus Ongoing Triple-therapy in long-term management of HIV disease

EUDRACT: 2007-006448-23
ISRCTN04857074

2. What if relevant new information becomes available?

Sometimes, during the course of a research project, vital new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to, or whether you should, continue with the study. If you decide not to carry on, your study doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your study doctor might consider it to be in your best interests to withdraw you from the study treatment. Your study doctor will explain the reasons and arrange for your care to continue. If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

3. What will happen if I don't want to carry on with the study?

You can decide that you no longer wish to receive study treatment at any time. We would however like to keep in contact with your doctor so that we can continue to receive information about your progress. If you do not wish us to have access to further information about your progress please inform your doctor. If you stop study treatment your doctor will continue to provide you with the best available care.

4. What if there is a problem?

In the event that something goes wrong and you are harmed during this study there are no special compensation arrangements. However, The Medical Research Council, UK (MRC) as the legal sponsor of this study, will give sympathetic consideration to claims for non-negligent harm suffered by a person as a result of a study, or other work supported by MRC. The hospital continues to have a duty of care to you, whether or not you are participating in an MRC supported study. The MRC does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of employees of hospitals. Negligence of NHS staff will be indemnified by the NHS or professional indemnity schemes. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for your legal costs.

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you. Participation in this study does not affect your normal rights to complain about any aspect of your treatment and care (contact number details can be obtained from your hospital).

If you have private medical insurance you should consult with your insurer before agreeing to take part.

5. Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it.

If you agree to join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from the MRC. They may also be looked at by representatives from the regulatory authorities to check that the study is being carried out correctly.

We will, if you give permission, contact your GP to notify them of your participation in the trial. We may also, if you give permission, contact other medical practitioners not involved in the research who are otherwise involved with your treatment to notify them of your participation in the trial.

We will ask if we can flag your records with the Office of National Statistics or trace them via the NHS Central Register so that if you move away or decide not to continue with the trial we will still be able to find out how you are doing. You will be asked a question about this on the consent form that you will have to sign before you are entered into the study.

6. What will happen to any samples I give?

Blood samples will be taken at clinic visits to monitor your progress and to check for any side effects as well as for the special tests required in the study protocol. At some visits we will specifically take an extra blood sample to keep in reserve in case future tests are needed. Any leftover blood and these extra blood samples will be stored securely and confidentially using a study number that will be assigned to you, rather than your name or other information that could identify you. As part of the consent we are asking for your permission to store these specimens for a period of 3 years after the study has finished so that we are able to use them for possible other tests in the future. These samples would be gifted by you to the research team. Until the study has been completed we will not know for sure what tests might usefully be done on these specimens. However, future tests would not involve any tests on your genes (DNA). Any future research on these samples taken will require further ethical review.

The researchers do not plan to contact you or your doctor with any results from future studies done on your stored specimens - this is because test are often experimental and should not be used to make decisions on treating your disease. Thus, while you will not benefit directly from any future research done, any results could be used to improve the treatment of HIV and its complications.

If you decide to provide blood for future research but change your mind later, you should inform your clinic that you do not want your samples used in future research. Your samples will then no longer be used.

7. What will happen to the results of the research study?

The results of the study will be published in a medical journal and on the website of the MRC Clinical Trials Unit – www.ctu.mrc.ac.uk. Interim results may be presented at clinical conferences. You will not be identified in any study report or publication.

A summary of the overall study results for patients who have participated will be produced once the study has been completed and analysed. A copy of the final publication will also be available to you through your study doctor.

8. Who is organising and funding the research?
The research is funded by the NHS Health Technology Assessment (HTA) programme, and is sponsored and conducted by the Medical Research Council.

The clinic you attend will be reimbursed for the additional costs incurred to them by your involvement in the study, such as the costs of blood tests and research nurse time. There will be no personal payments made to any member of staff for including you in this study.

9. Who has reviewed the study?
The study has been reviewed by the NHS HTA and the MRC. The study has also been given a favourable ethical opinion for conduct in the NHS by the Cambridgeshire 4 Research Ethics Committee.

10. Contact for Further Information
If you have any further questions concerning the study or if any problems arise during the study, please contact:

……on telephone number……..

and 24-hour telephone contact number ……

You may also find it helpful to contact i-Base, an independent information agency Treatment Information phone line 0808 800 6013 (open Mon-Wed 12-4pm). www.i-base.org.uk

Once again, we would like to thank you for taking the time to read this information and for considering taking part in this study.

APPENDIX 2: CONSENT FORM

(To be presented on local-headed paper)
Version 1.1, 25 March 2008

PIVOT: Protease Inhibitor monotherapy Versus Ongoing Triple -therapy in long-term management of HIV disease

EUDRACT: 2007-006448-23
ISRCTN04857074

Please initial box to agree

1. I confirm that I have read and understand the information sheet dated 25 March 2008 (Version 1.1) for the above study and have had the opportunity to ask questions and discuss it with my doctor. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals involved in the running of the study or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I give permission to be followed up through usual NHS mechanisms (e.g. Office for National Statistics). ☐
5. I agree to take part in PIVOT, the PI monotherapy study. ☐
6. **(Optional)** I agree that any left over blood stored during the study can be used by the research team in future tests. I understand that this will not involve any tests on my genes (DNA). These samples are gifted to the research team. ☐
7. **(Optional)** I agree to my GP being informed of my participation in this study. ☐

_____	_____	
Name of Participant	Date	Signature
_____	_____	
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	
Researcher	Date	Signature
_____	_____	
Witness (if applicable)	Date	Signature

3 copies: 1 for patient, 1 for researcher, 1 to be kept with hospital notes

APPENDIX 3: GP LETTER

(To be presented on local-headed paper)

[Date]

PIVOT: Protease Inhibitor monotherapy Versus Ongoing Triple-therapy in long-term management of HIV disease

EUDRACT: 2007-006448-23
ISRCTN04857074

Dear Dr _____

Your patient, _____ , has consented to participate in the trial named above and given permission to notify you of their participation in the trial. On _____ they were randomised to the _____ arm of the trial.

This is a randomised controlled clinical trial to compare a strategy of switching to boosted protease inhibitor (PI) monotherapy to continuing combination antiretroviral therapy (ART) for long-term management of HIV-infected patients.

This trial aims to determine whether a strategy of switching to PI monotherapy is non-inferior to continuing triple drug therapy in terms of the proportion of patients who maintain all their available drug treatment options after at least 3 years of follow-up.

Please find enclosed a copy of the patient information sheet for this trial and contraindicated medication.

You will be kept up-to-date with your patient's progress but if you have any concerns or questions regarding this study please contact the responsible doctor:

Dr _____ at _____(Hospital)

Tel: _____

Kind regards,

[Name]
[Position]

APPENDIX 4: PARTICIPATING SITES

UK Investigators

Dr Sharmin Obeyesekera Barking Hospital Sydenham Centre Upney Lane Barking		Dr Chloe Orkin Barts & The London NHS Trust Infection & Immunity Clinical Group King George V Block - Andrewes Unit St Bartholomews Hospital West Smithfield	
London	IG11 9LX	London	EC1 7BE
Dr Steve Taylor Birmingham Heartlands Hospital Directorate of Sexual Medicine and HIV Boardsley Green East		Dr Martin Fisher BSUH NHS Trust HIV/GUM Research The Elton John Centre Sussex House 1 Abbey Road	
Birmingham	B9 5SS	Brighton	BN2 1ES
Dr Humphrey Birley Cardiff Royal Infirmary Dept. of Genito-Urinary Medicine Newport Road		Dr Hitendra Thaker Castle Hill Hospital Infectious Diseases Castle Hill Road Cottingham	
Cardiff	CF24 0SZ	Hull	HU16 5JQ
Dr Gary Brook Central Middlesex Hospital Patrick Clements Clinic Acton Lane		Prof Brian Gazzard Chelsea and Westminster Hospital 4th Floor St Stephen's Centre 369 Fulham Road	
London	NW10 7NS	London	SW10 9NH
Dr Nigel O'Farrell Ealing Hospital Infection & Immunity Unit Pasteur Suite Uxbridge Road Southall		Dr Sunda Uthayakumar East and North Hertfordshire NHS Trust Genito-Urinary Medicine Woodlands Clinc Coreys Mill Lane	
Middlesex	UB1 3HW	Stevenage	SG1 4AB
Dr Sinnappah Jebakumar Edith Cavell Hospital Dept. of Sexual Health Clinic E Bretton Gate		Dr Shamela de Silva Farnham Road Hospital Farnham Road Guildford	
Peterborough	PE3 9GZ	Surrey	GU2 7LX
Dr Ray Fox Gartnavel General Hospital The Brownlee Centre Great Western Road		Dr Andrew DeBurgh-Thomas Gloucester Royal Hospital Hope House Dept. of GU & HIV Medicine Great Western Road	
Glasgow	G12 0YN	Gloucester	GL1 3NN

Dr David Chadwick James Cook University Hospital Dept. of Infection & Travel Medicine Marton Road	Dr Frank Post King's College Hospital Dept. of HIV/GUMedicine Weston Education Centre Cutcoombe Road Denmark Hill
Middlesbrough TS4 3BW	London SE5 9RS
Dr Adrian Palfreeman Leicester Royal Infirmary Genito-Urinary Medicine Infirmary Square	Dr Thambiah Balachandran Luton & Dunstable Hospital Dept. of Genito-Urinary Medicine Lewsey Road
Leicester LE1 5WW	Luton LU4 0DZ
Dr Vincent Lee Manchester Royal Infirmary Manchester Centre for Sexual Health Oxford Road	Dr Edmund Ong Newcastle General Hospital Infectious Diseases Westgate Road
Manchester M13 9WL	Newcastle upon Tyne NE4 6BE
Dr Ade Fakoya Newham University Hospital Dept. of Genito-Urinary Medicine Glen Road	Dr Edmund Wilkins North Manchester General Hospital Infectious Diseases Delaunays Road Crumpsall
London E13 8SL	Manchester M8 5RB
Dr Jonathan Ainsworth North Middlesex University Hospital T1 Coleridge Unit Sterling Way Edmonton	Dr Moses Kapembwa Northwick Park & St. Mark's Hospitals Dept. of GU/HIV Medicine Watford Road Harrow
London N18 1QX	Middlesex HA1 3UJ
Dr Brian Angus Oxford Radcliffe Hospitals NHS Trust Nuffield Department of Clinical Medicine Room 5801a, Level 5 Headley Way Headington	Dr Fabian Chen Royal Berkshire Hospital Genito-Urinary Medicine London Road Reading
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Dr Elbushra Herieka Royal Bournemouth Hospital Dept. of Genito-Urinary Medicine Castle Lane East	Prof Margaret Johnson Royal Free Hospital Dept. of Infection & Immunity Ian Charleson Centre Ground Floor Pond Street
Bournemouth BH7 7DW	London NW3 2QG
Dr David Dockrell Royal Hallamshire Hospital Infection, Inflammation & Immunity University of Sheffield School of Medicine & Biomedical Sciences L-Floor Glossop Road Sheffield S10 2JF	Dr Nick Beeching Royal Liverpool University Hospital Tropical & Infectious Disease Unit Prescot Street Liverpool L7 8XP

Dr Say Pheng Quah Royal Victoria Hospital Dept. of Genito-Urinary Medicine Level 3b Outpatients Centre Grosvenor Road Belfast		Dr John Day Southend Hospital Infectious Diseases & General Medicine Prittlewell Chase Westcliff on Sea	
Northern Ireland	BT12 6BA	Essex	SS0 0RY
Dr Mark Gompels Southmead Hospital Dept. of Immunology Westbury-on-Trym		Dr Phillip Hay St George's Hospital Clinical Infection Unit Jenner Wing Blackshaw Road Tooting	
Bristol	BS10 5NB	London	SW17 0QT
Dr Alan Winston St Mary's Hospital, London Clinical Trials Centre Winston Churchill Wing Praed Street		Dr Veerakathy Harindra St Mary's Hospital, Portsmouth Dept. of Genti-Urinary Medicine Milton Road	
London	W2 1NY	Portsmouth	PO3 6AD
Dr Ian Williams The Mortimer Market Centre, UCH Genito-Uninary Medicine University College Hospital The Mortimer Market Centre Off Capper Street		Dr Sris Allan University Hospital of Coventry & Warwickshire Dept. of Genito-Uninary Medicine Clifford Bridge Road Walsgrave	
London	WC1E 6AU	Coventry	CV2 2DX
Dr Joseph Arumainayagam Walsall Manor Hospital Dept. of Genito-Urinary Medicine Moat Road			
Walsall	WS2 9PS		

Ireland Investigators

Dr Patrick Mallon Mater Misericordiae University Hospital UCD School of Medicine & Medical Sciences Catherine McAuley Centre Nelson Street		Prof Fiona Mulchay St. James' Hospital Guide Clinic Hospital 5	
Dublin	7	Dublin	8

Italy Investigators

Dr Gianpiero D'Offizi IRCCS L. Spallanzani Via Portuense 292		Dr Giuseppe Tambussi Ospedale San Raffaele Centro San Luigi Divisione Malattie Infettive Via Stamira d'Ancona, 20	
Roma	00149	Milano	20157

APPENDIX 5: EQ-5D QUESTIONNAIRE

Describing your own health today

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety/Depression

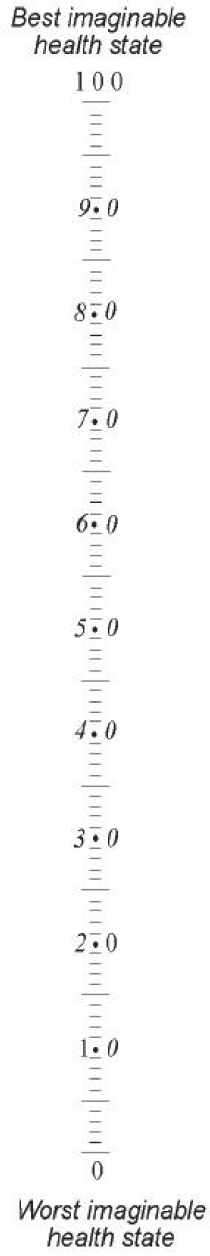
- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

Valuing your own health today

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



APPENDIX 6: MOS-HIV QUESTIONNAIRE

MOS – HIV QUALITY OF LIFE QUESTIONNAIRE

Date :	Clinic no:	Initials:	Date of birth:	Trial no:

INSTRUCTIONS

1. Please answer every question even though some questions may seem very similar to others.
2. Answer by placing a tick in the appropriate box. If you feel that the answer lies in between one possible response and another, please mark whichever box comes closest to the way you feel.
3. If you don't understand what a question means, please ask the Trial Nurse to explain or clarify it.

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE YOUR COOPERATION WILL BENEFIT YOURSELF, OTHER PEOPLE AND RESEARCH INTO HIV DISEASE.

1. In general, would you say your health is: (Please tick ONE box)

☐ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor

2. How much **bodily** pain have you generally had during **the past 4 weeks?** (Please tick ONE box)

☐ None ☐ Very Mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very Severe

3. During **the past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)? (Please tick ONE box)

☐ Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely

4. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (Please tick ONE box on each line)

	YES, Limited A Lot	YES, Limited A Little	NO, Not Limited At All
a. The kinds or amounts of **vigorous** activities you can do, like lifting heavy objects, running or participating in strenuous sports.	☐	☐	☐
b. The kinds or amounts of **moderate** activities you can do, like moving a table, carrying groceries or bowling.	☐	☐	☐
c. Walking uphill or climbing a few flights of stairs.	☐	☐	☐
d. Bending, lifting or stooping.	☐	☐	☐
e. Walking one hundred yards.	☐	☐	☐
f. Easting, dressing, bathing, or using the toilet.	☐	☐	☐

5. Does your health **keep** you from working at a job, doing work around the house or going to school? (Please tick ONE box)

☐ Yes ☐ No

6. Have you been unable to do **certain kinds or amounts** of work, housework, or schoolwork because of your health? (Please tick ONE box)

☐ Yes ☐ No

For each of the following questions, please tick the box for the one answer that comes closest to the way you have been feeling during the past 4 weeks. (Please tick ONE box on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
7. How much of the time, during the past 4 weeks, has your **health limited your social activities** (like visiting with friends or close relatives)?	☐	☐	☐	☐	☐	☐
8. How much of the time, during the past 4 weeks:	☐	☐	☐	☐	☐	☐
a. Have you been a very nervous person?	☐	☐	☐	☐	☐	☐
b. Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
c. Have you felt downhearted and low?	☐	☐	☐	☐	☐	☐
d. Have you been a happy person?	☐	☐	☐	☐	☐	☐
e. Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
9. How often during the past four weeks:						
a. Did you feel full of life?	☐	☐	☐	☐	☐	☐
b. Did you feel worn out?	☐	☐	☐	☐	☐	☐
c. Did you feel tired?	☐	☐	☐	☐	☐	☐
d. Did you have enough energy to do the things you wanted to do?	☐	☐	☐	☐	☐	☐
e. Did you feel weighed down by your health problems?	☐	☐	☐	☐	☐	☐
f. Were you discouraged by your health problems?	☐	☐	☐	☐	☐	☐
g. Did you feel despair over your health problems?	☐	☐	☐	☐	☐	☐
h. Were you afraid because of your health?	☐	☐	☐	☐	☐	☐
10. How much of the time, during the **past 4 weeks:**						
a. Did you have difficulty reasoning and solving problems, for example, making plans, making decisions, learning new things?	☐	☐	☐	☐	☐	☐
b. Did you forget things that happened recently, for example, where you put things and when you had appointments?	☐	☐	☐	☐	☐	☐
c. Did you have trouble keeping your attention on any activity for long?	☐	☐	☐	☐	☐	☐
d. Did you have difficulty doing activities involving concentration and thinking?	☐	☐	☐	☐	☐	☐

(Please tick ONE box on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
11. Please tick the box that best describes whether each of the following statements is true or false for you.	☐	☐	☐	☐	☐
a. I am somewhat ill.	☐	☐	☐	☐	☐
b. I am as healthy as anybody I know.	☐	☐	☐	☐	☐
c. My health is excellent.	☐	☐	☐	☐	☐
d. I have been feeling bad lately.	☐	☐	☐	☐	☐

12. How has the quality of your life been during the **past 4 weeks**? That is, how have things been going for you?
(Please tick ONE box)

- Very well; could hardly be better ☐
- Pretty good ☐
- Good and bad parts about equal ☐
- Pretty bad ☐
- Very bad; could hardly be worse ☐

13. How would you rate your physical health and emotional condition now compared to **4 weeks ago**?
(Please tick ONE box)

- Much better ☐
- A little better ☐
- About the same ☐
- A little worse ☐
- Much worse ☐

APPENDIX 7: TOXICITY TABLE

Division of AIDs table for grading severity of adult adverse experiences. Rockville: National Institute of Allergy and Infectious diseases, 1992.

GRADING OF ADVERSE EVENTS

ULN= upper limit of local reference range ("upper limit of normal")

	Grade 1	Grade 2	Grade 3	Grade 4
HAEMATOLOGICAL				
Haemoglobin g/dl	9.5-10.5	8.0-9.4	6.5-7.9	<6.5
Leucopoenia 10^9/l	3.0-3.9	2.0-2.9	1.9-1.0	<1.0
Neutrophils 10^9/l	1.00-1.50	0.75-0.99	0.50-0.74	<0.50
Platelets 10^9/l	75-99	50-74	20-49	<20 or diffuse petechiae
Prothrombin time	1.01-1.25x ULN	1.26-1.50x ULN	1.51-3.00x ULN	>3x ULN
Partial Prothrombin time	1.01-1.66x ULN	1.67-2.33x ULN	2.34-3.00x ULN	>3x ULN
Methaemoglobin	5-9.9%	10.0-14.9%	15.0-19.9%	>20%
BIOCHEMISTRY				
Hyponatraemia mmol/l	130-135	123-129	116-122	<116 or mental status change or seizures
Hypernatraemia	146150	151-157	158-165	>165 or mental status change or seizures
Hypokalaemia mmol/l	3.0-3.4	2.5-2.9 or replacement required	2.0-2.4 or replacement or hospitalisation	<2.0 or paresis or ileus or life-threatening arrhythmia
Hyperkalaemia	5.6-6.0	6.1-6.5	6.6-7.0	>7.0 or life-threatening arrhythmia
Hypocalcaemia mmol/l corrected for albumin	1.99-2.14	1.79-1.98	1.56-1.78	<1.56 or life-threatening arrhythmia
Hypercalcaemia corrected for albumin	2.70-2.93	2.94-3.19	3.20-3.44	>3.44 or life-threatening arrhythmias
Hypomagnesaemia mmol/l	0.60-0.75	0.45-0.59	0.30-0.44	<0.30 or life-threatening arrhythmias
Hypophosphataemia mmol/l	0.64-0.76	0.48-0.63	0.32-0.47	<0.32 or life-threatening arrythmias
Hypoglycaemia mmol/l	3.1-3.6	2.2-3.0	1.7-2.1	<1.7 or mental status change or coma
Hyperglycaemia (fasting)	6.5-9.0	9.1-14.0	14.1-28.0	>28.0 or ketoacidosis or seizures
Bilirubin mmol/l	1.1- 1.5x ULN	1.6- 2.5x ULN	2.6- 5.0x ULN	>5.0x ULN
AST or ALT or GGT U/l	1.26-2.5x ULN	2.6-5.0x ULN	5.1-10x ULN	>10x ULN
Alkaline phosphatase U/l	1.26-2.5x ULN	2.6-5.0x ULN	5.1-10x ULN	>10x ULN
Amylase U/l total or pancreatic or salivary	1.1-1.5x ULN	1.6-2.0x ULN	2.1-5.0x ULN	>5x ULN
Triglycerides (fasting) mmol/l	1.8- 2.2	2.3-5.6	5.7- 10.0	>10.0
Creatinine μmol/l	1.1- 1.5x UL N	1.6- 3.0x ULN	3.1- 6.0x ULN	>6.0x ULN or requires dialysis
Urea mmol/l	1.25-2.5x ULN	2.6- 5.0x ULN	5.1- 10.0x ULN	>10.0x ULN
CK U/l	1.1-2.0x ULN	2.1-4.0x ULN	4.1-6.0x ULN	>6x ULN
URINALYSIS				
Proteinuria	1+ or <0.3% or <3g/l or <1g/day loss	2-3+ or 0.3-1.0% or 3-10g/l or 1-2g/day loss	4+ or >1.0% or >10g/l or 2-3.5g/day loss	nephrotic syndrome or >3.5 g/day loss
Haematuria	microscopic only	gross, no clots	gross + clots	obstruction or requiring transfusion
GASTROINTESTINAL				
Stomatitis/mouth ulcers	mild discomfort, no limits on activity	some limits on eating or talking	eating/ talking very limited	requiring IV fluids
Nausea	mild discomfort, maintains reasonable intake	moderate discomfort, significantly decreased intake	severe discomfort, no significant intake	minimal intake
Vomiting	transient	occasional or moderate	orthostatic hypotension or IV fluids required	shock or hospitalisation required for IV fluids
Diarrhoea	transient or up to 4 loose stools/day	5-7 loose stools/day or nocturnal loose stools	orthostatic hypotension or >7 loose stools/day or requiring IV fluids	shock or hospitalisation required for IV fluids

	Grade 1	Grade 2	Grade 3	Grade 4
Clinical pancreatitis	mild abdominal pain, amylase <2.5x ULN, other causes excluded	moderate abdo. pain, amylase <2.5x ULN, other causes excluded	severe abdo. pain, amylase >2.5x ULN, hospitalised	severe abdo. pain, shock/ hypovolaemia, amylase>5x ULN, hosp.
NEUROLOGICAL				
Consciousness	difficulty in concentration or memory	mild confusion or lethargy <50% waking hours	disoriented or stupor >50% waking hours	coma or seizures
Mood	mild anxiety or depression	treatment required for anxiety or depression	needs assistance due to depression, mania or anxiety	acute psychosis or incapacitated or hospitalised
Headache	mild, no treatment	transient, moderate, requires treatment	severe, responds to first narcotic	intractable needing repeated narcotics
Activities of daily living	mild agitation or difficulty concentrating or confusion	some limitation ADL and minimal treatment required	treatment and assistance needed, severe agitation or confusion	toxic psychosis or hospitalisation
NEUROMUSCULAR				
Muscle strength	subjective weakness	mild objective signs, fully functional	objective weakness, limited function	paralysis
Clinical myopathy	minimal findings	moderate myalgia, may need NSAID, or difficulty climbing stairs or rising from sitting position, able to walk	moderate to severe myalgia needing NSAID, needing assistance walking or for general activities	severe myalgia unrelated to exercise requiring narcotics, unable to walk, or necrosis or oedema
Peripheral neuropathy	mild paraesthesia, numbness, pain or weakness, not treated	moderate paraesthesia, numbness or pain, objective weakness, requires analgesic	severe, narcotic required, interferes with normal activity	intolerable, incapacitating, unable to walk despite narcotics, paralysis
RESPIRATORY				
Bronchospasm	transient, no treatment, >70% peak flow or FEV1	requires treatment, normalises with bronchodilator, 50-70% peak flow or FEV1	no normalisation with bronchodilator, 25-50% peak flow or FEV1	cyanosis or intubated, <25% peak flow or FEV1
OTHER				
Fever, oral, >12 hours	37.7-38.5^{0}C	38.6-39.5^{0}C	39.6-40.5^{0}C	>40.5^{0}C
Fatigue	mild, no decrease in activity	25-50% decrease in activity	>50% decrease in activity, cannot work	unable to care for self
Hypersensitivity	pruritus without rash	localised urticaria	generalised urticaria or angioedema	anaphylaxis
Rash	erythema or pruritus	diffuse, maculopapular rash, dry desquamation	vesiculation, moist desquamation, ulceration	exfoliative dermatitis, mucous membrane involvement, or suspected Stevens-Johnson or erythema multiforme
Haemorrhage	microscopic or occult	mild, no transfusion	gross blood loss, transfused 1-2 units	massive blood loss, transfused >2 units
General	transient, mild, easily tolerated	moderate, discomfort, interrupts usual activity	severe, considerable interference with usual activity	incapacitating or life-threatening

APPENDIX 8: DIAGNOSTIC CRITERIA FOR SERIOUS AIDS-DEFINING ILLNESS

These criteria are based on the 1993 US Centers for Disease Control and Prevention criteria for category C disease (ref MMWR 1992; 41 [No RR-17]: 1-19), but excluding oesophageal candidiasis and chronic mucocutaneous herpes simplex virus infection. Events that meet either the presumptive criteria (if available) or definitive criteria will count as endpoints in this trial.

	PRESUMPTIVE CRITERIA	DEFINITIVE CRITERIA
CONSTITUTIONAL DISEASE		
HIV Wasting syndrome	Unexplained, involuntary weight loss >10% from baseline (week 0) PLUS persistent diarrhoea with 2 or more liquid stools/day > 1 month OR chronic weakness OR persistent fever > 1 month. Should exclude other causes such as cancer, TB, MAI, cryptosporidiosis or other specific enteritis.	none
INFECTIONS		
Candidiasis of bronchi, trachea or lungs	none	macroscopic appearance at bronchoscopy or autopsy, or histology or cytology/smear (not culture)
Coccidiodomycosis, disseminated or extrapulmonary	none	histology or cytology, culture or antigen detection from affected tissue
Cryptococcosis, meningitis or extrapulmonary	none	histology or cytology/microscopy, culture or antigen detection from affected tissue
Cryptosporidiosis	none	persistent diarrhoea > 1 month, histology or microscopy
CMV retinitis	Symptomatic or asymptomatic. Typical appearance on fundoscopy of discrete patches of retinal whitening, spreading along blood vessels, associated with vasculitis, haemorrhage and necrosis, confirmed by ophthalmologist.	none
CMV end-organ disease	none	compatible symptoms, plus histology or detection of antigen from affected tissue
CMV radiculomyelitis	Leg weakness and decreased reflexes or syndrome consistent with cord lesion presenting subacutely over daysto weeks. Myelogram shows no mass lesion. CSF shows >5 WBC with >50% polymorphs and no other pathogen or persistence of symptoms after appropriate treatment for other pathogens, OR CMV shown by PCR, antigen or culture.	none
CMV meningoencephalitis	Rapid (days to 1-4 weeks) syndrome with progressive delirium, cognitive impairment +/- seizures and fever (often with other CMV disease elsewhere). CT/MRI may show periventricular abnormalities with or without contrast enhancement. CSF may be normal or show evidence of CMV.	none
HSV visceral disease, e.g. bronchitis, pneumonitis, oesophagitis	none	symptoms, plus histology or culture or detection of antigen from affected tissue
Histoplasmosis, disseminated or extrapulmonary	none	symptoms, plus histology or culture or detection of antigen from affected tissues
Isosporiasis	none	persistent diarrhoea > 1 month, histology or microscopy
Leishmaniasis, visceral	none	symptoms, plus histology
Microsporidiosis	none	persistent diarrhoea > 1 month, histology or microscopy
MAC, and other atypical mycobacteriosis	Symptoms of fever, fatigue, anaemia or diarrhoea, plus AFBs seen in stool, blood, body fluid or tissue but not grown on culture, and no concurrent diagnosis of TB, except pulmonary	symptoms of fever, fatigue, anaemia or diarrhoea, culture from stool, blood, body fluid or tissue, except pulmonary
Tuberculosis, pulmonary	Symptoms of fever, dyspnoea, cough, weight loss or fatigue, plus AFBs seen in sputum or lavage or lung tissue but not grown in culture, plus responds to standard TB treatment	symptoms of fever, dyspnoea, cough, weight loss or fatigue, plus culture from sputum or lavage or lung tissue

	PRESUMPTIVE CRITERIA	DEFINITIVE CRITERIA
Tuberculosis, extrapulmonary	Symptoms, plus AFBs seen from affected tissue or blood but not grown in culture, concurrent diagnosis of pulmonary TB or responds to standard TB treatment	symptoms, plus culture from blood or affected tissue
PCP	Recent symptoms, plus typical CXR appearance if on PCP prophylaxis or any CX R appearance if not on prophylaxis and CD4+ <200, negative bronchoscopy if already treated for PCP for > 7 days or not done, no bacterial pathogens in sputum, and responds to PCP treatment	microscopy or histology
Extrapulmonary *pneumocystis*	none	symptoms plus microscopy or histology
Recurrent bacterial pneumonia	Second pneumonic episode within 1 year, new CXR appearance, symptoms and signs, diagnosed by a doctor	second pneumonic episode with 1 year, new CXR appearance, detection of bacterial pathogen
PML, Progressive multifocal leukoencephalopathy	Symptoms and brain scan consistent with PML, and no response to toxo treatment	histology
Recurrent salmonella septicaemia	none	second distinct episode, culture
Cerebral toxoplasmosis	Symptoms of focal intracranial abnormality or decreased consciousness, and brain scan consistent with lesion(s) having mass effect or enhanced by contrast, and either positive toxoplasma serology or responds to treatment clinically and by scan	histology or microscopy
Other extrapulmonary toxoplasmosis	none	symptoms plus histology or microscopy
NEOPLASMS		
KS, Kaposi's sarcoma	Typical appearance without resolution. clinicians who have seen few cases should not make presumptive diagnoses	Histology
Primary cerebral lymphoma	Symptom s consistent with lymphoma, at least one lesion with mass effect on brain scan, no response clinically and by scan to toxoplasma treatment	
B-cell, non-Hodgkin's lymphoma	none	histology
Cervical carcinoma, invasive	none	histology, not carcinoma-in-situ
NEUROLOGICAL		
HIV encephalopathy	Cognitive or motor dysfunction interfering with usual activity, progressive over weeks or months in the absence of another condition to explain the findings, should have brain scan +/- CSF to exclude other causes. should be grade 2 or worse in at least 2 domains by NARS (see below) excluding abnormal domains at trial entry	none
OTHER		
Indeterminate intracerebral lesion(s)	Neurological illness with evidence for an intracerebral lesion(s) by brain scan where the differential diagnosis is either cerebral toxoplasmosis, PML, cerebral lymphoma or HIV encephalopathy	none

ABBREVIATED NARS (Neuropsychiatric AIDS Rating Scale) grading for HIV ENCEPHALOPATHY

Adapted from: Price RW, Brew BJ. The AIDS dementia complex. J Infect Dis 1988; 158 (5): 1079-83, and Hughes CP, Berg L, Danziger WL. A new clinical scale for the staging of dementia. Brit J Psych 1982; 140: 566-92.

	Cognitive-Behavioural Domains					
	Orientation	**Memory**	**Motor**	**Behaviour**	**Problem solving**	**Activities of daily living**
NARS stage						
0.5	fully oriented	complains of memory problems	fully ambulatory slightly slowed movements	normal	has slight mental slowing	slight impairment in business dealings
1	fully oriented, may have brief periods of "spaciness	mild memory problems	balance, co-ordination and handwriting difficulties	more irritable, labile or apathetic, withdrawn	difficulty planning and completing work	can do simple daily tasks, may need prompting
2	some disorientation	memory moderately impaired, new learning impaired	ambulatory but may require walking aid	some impulsivity or agitated behaviour	severe impairment, poor social judgement, gets lost easily	needs assistance with ADLs
3	frequent disorientation	severe memory loss, only fragments of memory remain	ambulatory with assistance	may have organic psychosis	judgement very poor	cannot live independently
4	confused and disoriented	virtually no memory	bedridden	mute and unresponsive	no problem solving ability	nearly vegetative

APPENDIX 9: DIAGNOSTIC CRITERIA FOR SERIOUS NON-AIDS-DEFINING ILLNESS

These criteria are based on those used in long term clinical endpoint trials by the INSIGHT research network, with additional criteria for acute liver failure, severe acute pancreatitis, severe lactic acidaemia, severe facial lipoatrophy and severe peripheral neuropathy that are based on standard toxicity criteria or definitions developed in case-definition studies.

	DIAGNOSTIC CRITERIA
Serious Non-AIDS event	
Acute myocardial infarction (MI)	A or (B+C) or (B+D): (A) Acute MI demonstrated as the cause of death on autopsy; (B) Occurrence of a compatible clinical syndrome, including symptoms (e.g. chest pain) consistent with myocardial ischaemia; (C) Development of (i) evolving new Q waves, or (ii) evolving ST elevation, based on at least two EKGs taken during the same hospital admission; (D) Diagnostic elevation of CK-MB to more than twice the upper limit of normal in the laboratory performing the study, or diagnostic elevation of troponin above ULN.
Coronary artery disease requiring invasive procedures	Written report in medical record detailing procedure performed for treating coronary artery disease, including: coronary artery bypass graft, coronary artery stent implant, coronary artherectomy, and percutaneous tran sluminal angioplasty.
Cirrhosis	(A+B+C) or (A+B+D) or (A+B+E) or F or G: (A) Clinical evidence of cirrhosis, with at least one of the following: ascites, hepatic encephalopathy, gastric or oesophageal varices, or signs of portal hypertension on endoscopy, without another explanation for these symptoms; (B) At least one of the following: Increased PT or INR above ULN, serum AST > serum ALT, platelet count <150,000; (C) albumin <3 g/dL or <30 g/L; (D) A positive result on an approved diagnostic fibrosis panel, e.g. Fibrosure/Fibrotest; (E) A positive result on transient elastography (Fibroscan) consistent with cirrhosis; (F) MRI, CT or ultrasound imaging consistent with cirrhosis (e.g. nodular liver, reversal of flow in portal vein); (G) Histologic evidence obtained by liver biopsy or autopsy.
Acute liver failure	ALT or AST greater than 5 times ULN, with clinical jaundice and encephalopathy.
End-stage renal disease	A or B or C: (A) Haemodialysis or pertitoneal dialysis for a period of at least three months, documented in a clinical note; (B) A kidney transplant, documented in a clinical note; (C) two consecutive measurements of serum creatinine clearance rate < 15 ml/min per 1.73 m^2 calculated using the Cockcroft-Gault equation.
Stroke	(A+D) or (A+B) or (A+C) or D or E: (A) Acute onset with a clinically compatible course, including unequivocal objective findings of a localising neurologic deficit; (B) CT or MRI compatible with diagnosis of stroke and current neurologic signs and symptoms; (C) Positive lumbar puncture compatible with subarachnoid haemorrhage; (D) Stroke diagnosed as cause of death at autopsy; (E) Death certificate or death note from medical record listing stroke as cause of death.
Severe acute pancreatitis	Severe abdominal pain requiring hospitalisation and blood amylase levels greater than 2.5 times the upper limit of normal.
Severe lactic acidaemia	Two consecutive measures of peripheral blood lactate > 5 mmol/l (45 mg/dl) or demonstrated lactic acidosis (arterial blood pH < 7.34, blood bicarbonate < 20 mmol/l and blood lactate levels above normal range).
Severe facial lipoatrophy	Facial fat loss that is considered to be obvious to both patient and clinician and that is considered by the clinician to have the characteristic appearance of HIV-associated lipoatrophy.
Severe peripheral neuropathy	Severe pain, numbness or tingling in the feet and/or legs that interferes with normal activities and requires narcotic analgesia for control.
Non-AIDS malignancy (excluding Kaposi's sarcoma (KS), lymphoma, invasive cervical cancer)	Diagnosis of cancer other than lymphoma, KS or invasive cervical cancer and a written report in the medical record from the hospitalisation during which the diagnosis was established, or in a pathology report that established the diagnosis, or in an autopsy report.

APPENDIX 10: PROTEASE INHIBITOR INFORMATION

BNF November 2007 (www.bnf.org)

Cautions

Protease inhibitors are associated with hyperglycaemia and should be used with caution in diabetes (see Lipodystrophy Syndrome). Caution is also needed in patients with haemophilia who may be at increased risk of bleeding. Protease inhibitors should be used with caution in hepatic impairment (BNF Appendix 2); the risk of hepatic side-effects is increased in patients with chronic hepatitis B or C. Atazanavir, darunavir, fosamprenavir, and tipranavir may be used at usual doses in patients with renal impairment, but other protease inhibitors should be used with caution in renal impairment (BNF Appendix 3). Protease inhibitors should also be used with caution during pregnancy (BNF Appendix 4).

Side-effects

Side-effects of the protease inhibitors include gastro-intestinal disturbances (including diarrhoea, nausea, vomiting, abdominal pain, flatulence), anorexia, hepatic dysfunction, pancreatitis; blood disorders including anaemia, neutropenia, and thrombocytopenia; sleep disturbances, fatigue, headache, dizziness, paraesthesia, myalgia, myositis, rhabdomyolysis; taste disturbances; rash, pruritus, Stevens-Johnson syndrome, hypersensitivity reactions including anaphylaxis; see also notes above for lipodystrophy and metabolic effects (Lipodystrophy Syndrome), and Osteonecrosis.

Lipodystrophy Syndrome

Metabolic effects associated with antiretroviral treatment include fat redistribution, insulin resistance and dyslipidaemia; collectively these have been termed lipodystrophy syndrome.

Fat redistribution (with loss of subcutaneous fat, increased abdominal fat, 'buffalo hump' and breast enlargement) is associated with regimens containing protease inhibitors and nucleoside reverse transcriptase inhibitors. Stavudine, and to a lesser extent zidovudine, are associated with a higher risk of lipoatrophy and should be used only if alternative regimens are not suitable.

Dyslipidaemia (with adverse effects on body lipids) is associated with antiretroviral treatment, particularly with protease inhibitors. Protease inhibitors are associated with insulin resistance and hyperglycaemia. Plasma lipids, blood glucose and the usual risk factors for atherosclerotic disease should be taken into account before prescribing regimens containing a protease inhibitor; patients receiving protease inhibitors should be monitored for changes in plasma lipids and blood glucose.

Sub-sections:

AMPRENAVIR
ATAZANAVIR
DARUNAVIR
FOSAMPRENAVIR
INDINAVIR
LOPINAVIR WITH RITONAVIR
NELFINAVIR
RITONAVIR
SAQUINAVIR
TIPRANAVIR

AMPRENAVIR		
Interactions	Liver disease	Avoid oral solution due to high propylene glycol content; without low-dose ritonavir, reduce dose of amprenavir capsules to 450 mg every 12 hours in moderate hepatic impairment and reduce dose to 300 mg every 12 hours in severe impairment
	Renal impairment	Mild-moderate: Use oral solution with caution due to high propylene glycol content Severe: Avoid oral solution
	Pregnancy	Avoid oral solution due to high propylene glycol content; manufacturer advises use capsules only if potential benefit outweighs risk
Indications	HIV infection in combination with other antiretroviral drugs in patients previously treated with other protease inhibitors	
Cautions	Rash. Rash may occur, usually in the second week of therapy; discontinue permanently if severe rash with systemic or allergic symptoms or, mucosal involvement; if rash mild or moderate, may continue without interruption—rash usually resolves within 2 weeks and may respond to antihistamines	
Contra-indications	Breast-feeding not advised in HIV infection	
Side-effects	see notes above; also reported, rash including rarely Stevens-Johnson syndrome (see also above); tremors, oral or perioral paraesthesia, mood disorders including depression	
Dose	Agenerase®(GSK) Capsules, ivory, amprenavir 50 mg. Excipients include vitamin E 36 units/50 mg amprenavir (avoid vitamin E supplements) Dose adult and adolescent over 12 years, body-weight over 50 kg, 1.2 g every 12 hours; adult and adolescent over 12 years, body-weight under 50 kg and child 4–12 years, 20 mg/kg every 12 hours (max. 2.4 g daily) With low-dose ritonavir, adult and adolescent over 12 years, body-weight over 50 kg, amprenavir 600 mg every 12 hours with ritonavir 100 mg every 12 hours Oral solution, grape-bubblegum- and peppermint-flavoured, amprenavir 15 mg/mL. Excipients include vitamin E 46 units/mL (avoid vitamin E supplements), propylene glycol 550 mg/mL (see Excipients) Electrolytes: K+ 26 micromol/mL, Na+ 174 micromol/mL Dose adult and child over 4 years, 17 mg/kg every 8 hours (max. 2.8 g daily); child under 4 years not recommended Note: The bioavailability of Agenerase® oral solution is lower than that of capsules; the two formulations are not interchangeable on a milligram-for-milligram basis	
ATAZANAVIR		
Interactions	Liver disease	Manufacturer advises caution in mild hepatic impairment; avoid in moderate to severe hepatic impairment
	Pregnancy	Manufacturer advises use only if potential benefit outweighs risk; theoretical risk of hyperbilirubinaemia in neonate if used at term
Indications	HIV infection in combination with other antiretroviral drugs in patients previously treated with antiretrovirals	
Cautions	see notes above; also concomitant use with drugs that prolong PR interval; cardiac conduction disorders; predisposition to QT interval prolongation (including electrolyte disturbances, concomitant use of drugs that prolong QT interval); interactions: BNF Appendix 1 (atazanavir)	
Contra-indications	Breast-feeding not advised in HIV infection	
Side-effects	see notes above; also peripheral neurological symptoms; less commonly mouth ulcers, hypertension, syncope, chest pain, dyspnoea, abnormal dreams, amnesia, depression, anxiety, weight changes, increased appetite, gynaecomastia, nephrolithiasis, urinary frequency, haematuria, proteinuria, arthralgia, and alopecia; rarely hepatosplenomegaly, oedema, palpitation, and abnormal gait	
Dose	with low-dose ritonavir and food, adult over 18 years, 300 mg once daily with ritonavir 100 mg once daily	
	Reyataz®(Bristol-Myers Squibb) Capsules, atazanavir (as sulphate) 100 mg (dark blue/white); 150 mg (dark blue/light blue); 200 mg (dark blue),	
DARUNAVIR		
Interactions	Liver disease	Manufacturer advises caution in mild to moderate hepatic impairment; avoid in severe hepatic impairment—no information available

	Pregnancy	Manufacturer advises use only if potential benefit outweighs risk
Indications	HIV infection (that has not responded to treatment with other protease inhibitors) in combination with other antiretroviral drugs	
Cautions	see notes above; also sulpho namide sensitivity	
Contra-indications	Breast-feeding not advised in HIV infection	
Side-effects	see notes above; also myocardial infarction, transient ischaemic attack, syncope, tachycardia, hypertension, flushing, peripheral oedema, dyspnoea, cough, hiccups, peripheral neuropathy, anxiety, confusion, memory impairment, mood changes, abnormal coordination, weight gain, hyperthermia, hypothyroidism, osteoporosis, gynaecomastia, erectile dysfunction, dysuria, polyuria, nephrolithiasis, renal failure, hyponatraemia, arthralgia, keratoconjuntivitis sicca, salivation changes, mouth ulcers, increased sweating, and alopecia	
Dose	With low-dose ritonavir, adult over 18 years, 600 mg twice daily Missed dose If a dose is more than 6 hours late, the missed dose should not be taken and the next dose should be taken at the normal time	
	Prezista®(Janssen-Cilag) Tablets , orange, f/c, darunavir (as ethanolate) 300 mg	
FOSAMPRENAVIR		
Interactions	Note Fosamprenavir is a pro-drug of amprenavir	
Indications	HIV infection in combination with other antiretroviral drugs	
Cautions	see notes above and under Amprenavir	
Contra-indications	Breast-feeding not advised in HIV infection	
Side-effects	see notes above and under Amprenavir	
Dose	with low-dose ritonavir, adult over 18 years, 700 mg twice daily Note 700 mg fosamprenavir is equivalent to approx. 600 mg amprenavir	
	Telzir®(GSK) Tablets , f/c, pink, fosamprenavir (as calcium) 700 mg Oral suspension , fosamprenavir (as calcium) 50 mg/mL, (grape-bubblegum-and peppermint-flavoured) (with 10-mL oral syringe)	
INDINAVIR		
Interactions	Liver disease	Increased risk of nephrolithiasis; reduce dose to 600 mg every 8 hours in mild to moderate hepatic impairment; not studied in severe impairment
	Pregnancy	Toxicity in *animal* studies; manufacturer advises use only if potential benefit outweighs risk; theoretical risk of hyperbilirubinaemia and renal stones in neonate if used at term
Indications	HIV infection in combination with nucleoside reverse transcriptase inhibitors	
Cautions	see notes above; also ensure adequate hydration (risk of nephrolithiasis especially in children); patients at risk of nephrolithiasis (monitor for nephrolithiasis); avoid in porphyria (section 9.8.2); interactions: BNF Appendix 1 (indinavir)	
Contra-indications	Breast-feeding not advised in HIV infection	
Side-effects	see notes above; also reported, dry mouth, hypoaesthesia, dry skin, hyperpigmentation, alopecia, paronychia, interstitial nephritis (with medullary calcification and cortical atrophy in asymptomatic severe leucocyturia), nephrolithiasis (may require interruption or discontinuation; more frequent in children), dysuria, haematuria, crystalluria, proteinuria, pyuria (in children), pyelonephritis; haemolytic anaemia	
Dose	800 mg every 8 hours; child and adolescent4–17 years, 500 mg/m2 every 8 hours (max. 800 mg every 8 hours); child under 4 years, safety and efficacy not established Crixivan®(MSD) Capsules , indinavir (as sulphate), 200 mg; 400 mg, Counselling Administer 1 hour before or 2 hours after a meal; may be administered with a low-fat light meal; in combination with didanosine tablets, allow 1 hour between each drug (antacids in didanosine tablets reduce absorption of indinavir); in combination with low-dose ritonavir, give with food Note Dispense in original container (contains dessicant)	
LOPINAVIR WITH RITONAVIR		
Interactions	Liver disease	Avoid oral solution because of propylene glycol content; manufacturer advises avoid capsules and tablets in severe hepatic impairment
	Renal impairment	Avoid oral solution due to propylene glycol content; use capsules and tablets with caution in severe impairment

	Pregnancy	Avoid oral solution due to high propylene glycol content; manufacturer advises use capsules and tablets only if potential benefit outweighs risk (toxicity in animal studies)
Indications	HIV infection in combination with other antiretroviral drugs	
Cautions	see notes above; concomitant use with drugs that prolong QT interval; pancreatitis (see below); interactions: BNF Appendix 1 (lopinavir, ritonavir) Pancreatitis Signs and symptoms suggestive of pancreatitis (including raised serum lipase) should be evaluated—discontinue if pancreatitis diagnosed	
Contra-indications	Breast-feeding not advised in HIV infection	
Side-effects	see notes and Cautions above; also electrolyte disturbances in children; less commonly dysphagia, appetite changes, weight changes, cholecystitis, hypertension, myocardial infarction, palpitation, thrombophlebitis, vasculitis, chest pain, oedema, dyspnoea, cough, agitation, anxiety, amnesia, ataxia, hypertonia, confusion, depression, abnormal dreams, extrapyramidal effects, neuropathy, influenza-like syndrome, Cushing's syndrome, hypothyroidism, menorrhagia, amenorrhoea, sexual dysfunction, breast enlargement, dehydration, nephritis, hypercalciuria, lactic acidosis, arthralgia, hyperuricaemia, abnormal vision, otitis media, tinnitus, dry mouth, sialadenitis, mouth ulceration, periodontitis, acne, alopecia, dry skin, sweating, skin discoloration, nail disorders, rarely prolonged PR interval	
Dose	Kaletra®(Abbott) Capsules , orange, lopinavir 133.3 mg, ritonavir 33.3 mg Dose adult and child over 2 years with body surface area of 1.4 m2 or greater, 3 capsules twice daily with food; child over 2 years with body surface area less than 1.4 m2, oral solution preferred; if oral solution inappropriate and body surface area 0.4–0.75 m2, 1 capsule twice daily, body surface area 0.8–1.3 m2, 2 capsules twice daily Tablets , yellow, f/c, lopinavir 200 mg, ritonavir 50 mg Dose adult and child with body surface area greater than 1.3 m2 or body-weight 40 kg and over, 2 tablets twice daily Oral solution , lopinavir 400 mg, ritonavir 100 mg/5 mL Excipients include propylene glycol 153 mg/mL (see Excipients), alcohol 42% Dose adult and adolescent, 5 mL twice daily with food; child over 2 years 2.9 mL/m2 twice daily with food, max. 5 mL twice daily; child under 2 years, safety and efficacy not established Note 5 mL oral solution = 3 capsules = 2 tablets; where appropriate, capsules may be used instead of oral solution	
NELFINAVIR		
Interactions	Liver disease	No information available—manufacturer advises caution
	Renal impairment	No information available—manufacturer advises caution
	Pregnancy	No information available—manufacturer advises use only if potential benefit outweighs risk
Indications	HIV infection in combination with other antiretroviral drugs	
Cautions	see notes above; interactions: see BNF Appendix 1 (nelfinavir)	
Contra-indications	Breast-feeding not advised in HIV infection	
Side-effects	see notes above; also reported, fever	
Dose	1.25 g twice daily or 750 mg 3 times daily; child 3–13 years, initially 50–55 mg/kg twice daily (max. 1.25 g twice daily) or 25–30 mg/kg 3 times daily (max. 750 mg 3 times daily)	
	Viracept®(Roche) Tablets , blue, f/c, nelfinavir (as mesilate) 250 mg Oral powder , nelfinavir (as mesilate) 50 mg/g. Excipients include aspartame (section 9.4.1) Counselling Powder may be mixed with water, milk, formula feeds or pudding; it should not be mixed with acidic foods or juices owing to its taste	
RITONAVIR		
Interactions	Hepatic impairment	Avoid in decompensated liver disease; in severe hepatic impairment without decompensation, use 'booster' doses with caution (avoid treatment doses)
	Pregnancy	Manufacturer advises use only if potential benefit outweighs risk—no information available
Indications	HIV infection in combination with nucleoside reverse transcriptase inhibitors; low doses used to increase effect of some protease inhibitors	
Cautions	see notes above; avoid in porphyria (section 9.8.2); pancreatitis (see below); interactions: see BNF Appendix 1 (ritonavir). Pancreatitis Signs and symptoms suggestive of pancreatitis (including raised serum lipase) should be evaluated—discontinue if pancreatitis diagnosed	

Contra-indications	Breast-feeding not advised in HIV infection	
Side-effects	see notes and Cautions above; also diarrhoea (may impair absorption—close monitoring required), vasodilatation, cough, throat irritation, anxiety, perioral and peripheral paraesthesia, hyperaesthesia, fever, decreased blood thyroxine concentration, electrolyte disturbances, raised uric acid, dry mouth, mouth ulcers, and sweating; less commonly increased prothrombin time and dehydration; syncope, postural hypotension, seizures, menorrhagia, and renal failure also reported	
Dose	initially 300 mg every 12 hours for 3 days, increased in steps of 100 mg every 12 hours over not longer than 14 days to 600 mg every 12 hours; child over 2 years initially 250 mg/m2 every 12 hours, increased by 50 mg/m2 at intervals of 2–3 days to 350 mg/m2 every 12 hours (max. 600 mg every 12 hours). Low-dose booster to increase effect of other protease inhibitors, 100–200 mg once or twice daily	
	Norvir®(Abbott) Capsules , ritonavir 100 mg Excipients include alcohol 12% Oral solution , sugar-free, ritonavir 400 mg/5 mL Counselling Oral solution contains 43% alcohol; bitter taste can be masked by mixing with chocolate milk; do not mix with water, measuring cup must be dry	
	With lopinavir: See under Lopinavir with ritonavir	
SAQUINAVIR		
Interactions	Hepatic impairment	Manufacturer advises caution in moderate hepatic impairment; avoid in severe impairment
	Renal impairment	severe Dose adjustment possibly required
Indications	HIV infection in combination with other antiretroviral drugs	
Cautions	see notes above; concomitant use of garlic (avoid garlic capsules—reduces plasma-saquinavir concentration); interactions: BNF Appendix 1 (saquinavir)	
Contra-indications	Breast-feeding not advised in HIV infection	
Side-effects	see notes above; also dyspnoea, increased appetite, peripheral neuropathy, convulsions, changes in libido, renal impairment, dry mouth, and alopecia	
Dose	with low-dose ritonavir, adult and adolescent over 16 years, 1 g every 12 hours Invirase®(Roche) Capsules , brown/green, saquinavir (as mesilate) 200 mg Tablets , orange, f/c, saquinavir (as mesilate) 500 mg	
TIPRANAVIR		
Interactions	See BNF Appendix 1	
Indications	HIV infection resistant to other protease inhibitors, in combination with other antiretroviral drugs in patients previously treated with antiretrovirals	
Cautions	see notes above; also patients at risk of increased bleeding from trauma, surgery or other pathological conditions; concomitant use of drugs that increase risk of bleeding; interactions: BNF Appendix 1 (tipranavir). Hepatotoxicity Potentially life-threatening hepatotoxicity reported; monitor liver function before treatment then on weeks 2, 4 and 8 of treatment, then every 2–3 months (every 2 weeks for first 3 months then monthly in those with hepatic impairment (BNF Appendix 2)). Discontinue if signs or symptoms of hepatitis develop or if liver-function abnormality develops (consult product literature)	
Contra-indications **Side-effects**	Breast-feeding not advised in HIV infection see notes above; also dyspnoea, anorexia, peripheral neuropathy, influenza-like symptoms, renal impairment and photosensitivity; rarely dehydration	
Dose	With low-dose ritonavir, 500 mg twice daily; child safety and efficacy not established	
	Aptivus®(Boehringer Ingelheim) Capsules , pink, tipranavir 250 mg Excipients include ethanol 100 mg per capsule	

APPENDIX 11: JOINT BRITISH SOCIETIES CARDIOVASCULAR RISK PREDICTION CHARTS

BNF September 2006 (www.bnf.org)

Cardiovascular Risk Prediction Charts

Heart 2005; **91**(Suppl V): v1–v52

How to use the Cardiovascular Risk Prediction Charts for Primary Prevention

These charts are for estimating cardiovascular disease (CVD) risk (non-fatal myocardial infarction and stroke, coronary and stroke death and new angina pectoris) for individuals who have **not** already developed coronary heart disease (CHD) or other major atherosclerotic disease. They are an aid to making clinical decisions about how intensively to intervene on lifestyle and whether to use antihypertensive, lipid lowering and anti-platelet medication, but should **not replace clinical judgment**.

- The use of these charts is **not appropriate** for patients who have existing diseases which already put them at high risk such as:
  - coronary heart disease or other major atherosclerotic disease;
  - familial hypercholesterolaemia or other inherited dyslipidaemias;
  - renal dysfunction including diabetic nephropathy;
  - type 1 and 2 diabetes mellitus.
- The charts should **not** be used to decide whether to introduce antihypertensive medication when blood pressure is persistently at or above 160/100 mmHg or when target organ damage due to hypertension is present. In both cases antihypertensive medication is recommended regardless of CVD risk. Similarly the charts should **not** be used to decide whether to introduce lipid-lowering medication when the ratio of serum total to HDL cholesterol exceeds 6. Such medication is generally then indicated regardless of estimated CVD risk.
- To estimate an individual's absolute 10-year risk of developing CVD choose the chart for his or her sex, lifetime smoking status and age. Within this square identify the level of risk according to the point where the coordinates for systolic blood pressure and the ratio of total cholesterol to high density lipoprotein (HDL) cholesterol meet. If no HDL cholesterol result is available, then assume this is 1.0 mmol/litre and the lipid scale can be used for total cholesterol alone.
- Higher risk individuals (red areas) are defined as those whose 10-year CVD risk exceeds 20%, which is approximately equivalent to the coronary heart disease risk of > 15% over the same period.
- The chart also assists in identifying individuals whose 10-year CVD risk is moderately increased in the range 10–20% (orange areas) and those in whom risk is lower than 10% over 10 years (green areas).
- Smoking status should reflect lifetime exposure to tobacco and not simply tobacco use at the time of assessment. For example, those who have given up smoking within 5 years should be regarded as current smokers for the purposes of the charts.
- The initial blood pressure and the first random (non-fasting) total cholesterol and HDL cholesterol can be used to estimate an individual's risk. However, the decision on using drug therapy should generally be based on repeat risk factor measurements over a period of time.

(Continued over)

- Men and women do not reach the level of risk predicted by the charts for the three age bands until they reach the ages 49, 59, and 69 years respectively. The charts will overestimate current risk most in the under 40s. Clinical judgement must be exercised in deciding on treatment in younger patients. However, it should be recognised that blood pressure and cholesterol tend to rise most and HDL cholesterol to decline most in younger people already with adverse levels. Left untreated, their risk at the age 49 years is likely to be higher than the projected risk shown on the age-under-50-years chart. From age 70 years the CVD risk, especially for men, is usually ≥ 20% over 10 years and the charts will underestimate true total CVD risk.

- These charts (and all other currently available methods of CVD risk prediction) are based on groups of people with **untreated** levels of blood pressure, total cholesterol and HDL cholesterol. In patients already receiving antihypertensive therapy in whom the decision is to be made about whether to introduce lipid-lowering medication, or vice versa, the charts can only act as a guide. Unless recent pre-treatment risk factor values are available it is generally safest to assume that CVD risk is higher than that predicted by current levels of blood pressure or lipids on treatment.

- CVD risk is also higher than indicated in the charts for:

  - those with a family history of premature CVD or stroke (male first-degree relatives aged < 55 years and female first-degree relatives aged < 65 years) which increases the risk by a factor of approximately 1.3;

  - those with raised triglyceride levels (> 1.7 mmol/litre);

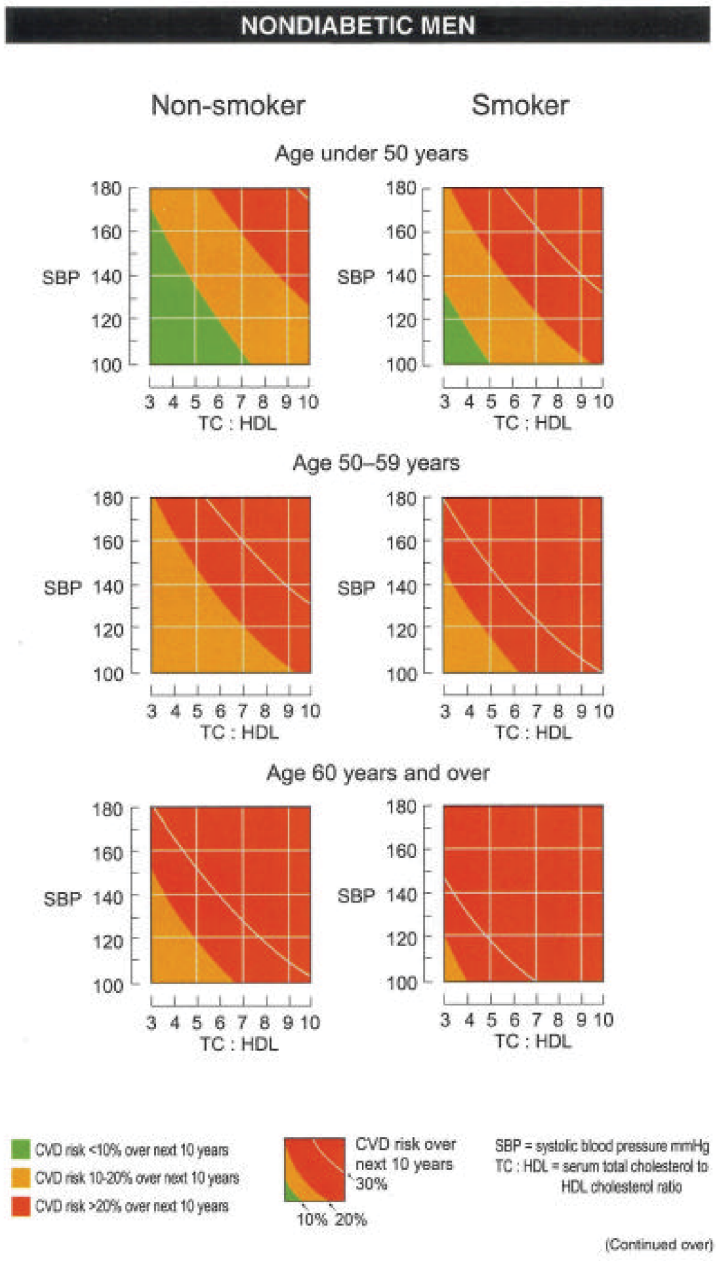
  - women with premature menopause;

  - those who are not yet diabetic, but have impaired fasting glycaemia (6.1–6.9 mmol/litre) or impaired glucose tolerance (2 hour glucose ≥ 7.8 mmol/litre but < 11.1 mmol/litre in an oral glucose tolerance test).

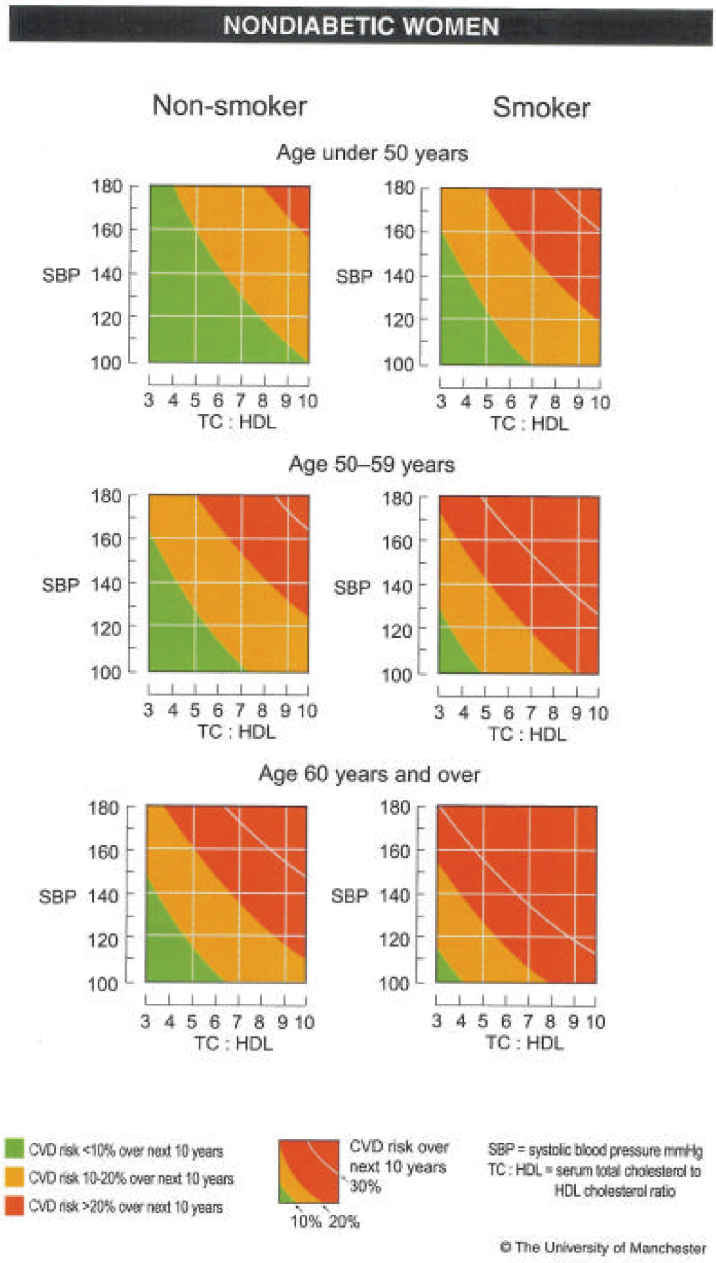
- The charts have not been validated in ethnic minorities and in some may underestimate CVD risk. For example, in people originating from the Indian subcontinent it is safest to assume that the CVD risk is higher than predicted from the charts (1.4 times).

- An individual can be shown on the chart the direction in which his or her risk of CVD can be reduced by changing smoking status, blood pressure, or cholesterol, but it should be borne in mind that the estimate of risk is for a group of people with similar risk factors and that within that group there will be considerable variation in risk. It should also be pointed out in younger people that the estimated risk will generally not be reached before the age of 50, if their current blood pressure and lipid levels remain unchanged. The charts are primarily to assist in directing intervention to those who typically stand to benefit most.

(Continued over)



(Continued over)



APPENDIX 12: LABORATORY METHODS & SPECIMEN STORAGE

Storage specimens
4mls of EDTA blood to be taken for storage at baseline, Week 4 (PI monotherapy arm only), Week 12 and then annually. An additional sample will be taken at any visit where a second VL test is performed as confirmation of viral rebound.

These samples will be collected in a 1x 4ml EDTA collection tube, processed within 4 hours from the time of blood draw. Any leftover blood will be separated, and the plasma stored in 1ml aliquots at -70°C in case future testing is required.

Stored blood samples will be labelled with the patient's trial number and draw date. Samples must be processed, stored and documented until collection and centralisation of the samples at the central repository at Mill Hill. Shipping of specimens from sites to the central repository will be conducted annually.

Central resistance testing
In order to be able to extrapolate the findings beyond the 5-year period of the trial, it will be important to document that the patients on PI monotherapy who remain virologically suppressed during the trial have full virological suppression (to the same extent as patients on triple-therapy). Therefore, a single sample will be sent for testing by a very low copy assay (<5 copies/ml) at a central laboratory in all patients who have VL <50 copies/ml on conventional testing at the last follow-up visit of the trial.

Therapeutic Drug Monitoring
Patients in the PI monotherapy arm will have a blood sample taken at the Week 4 visit for measurement of the trough level of the PI. Samples in the UK will be sent for TDM processing via normal hospital procedures to Delphic Diagnostics. Results will be made available to the sites within approximately 2 weeks of sample collection.

Arrangements for TDM at non-UK sites are to be confirmed.

APPENDIX 13: NEUROCOGNITIVE ASSESSMENT TOOLS

Hopkins Verbal Learning test-revised (HVLT-R)
For this test the examiner will read aloud a list of 12 words and immediately after finishing that, the participant will be asked to freely recall them. The test is performed a further two times asking the participant to recall the words immediately after each reading. After the third exercise of free recall is completed, the examiner will read aloud a list of 24 words which includes the 12 words used for the previous part of the test. The participant will be asked to answer "yes" or "no" as the examiner reads each word if s/he recognises that word as one of the words included in the original 12 word list used for the first part of the test. The list of 24 words to be used in the second part of the test (recognition trial) includes, apart from the 12 "target words", 6 words that are categorically related to the target words. It also includes 6 unrelated words. After completing all the other neuropsychological tests and the MOS-HIV quality of life questionnaire (i.e. after about 15-20 minutes) the examiner will ask the participant to recall the words read at the beginning of the test (without the examiner repeating the list again) in order to assess delayed memory.

Each word recalled is scored during the immediate free recalling section of the test (range 0 – 36) and during the delayed recall test (range 0 – 12). In addition, the total number of correct responses is scored from the recognition section of the test. To control for the effect of practising on repeated administration a different version of the test, with different lists of words, will be used at each visit. A number of different versions of the test are commercially produced (Psychological Assessment Resources Inc).

Sample of Hopkins verbal learning test

HOPKINS VERBAL LEARNING TEST (HVLT) - FORM 1

Instructions: Read the list of 12 words in Part A (at a rate of 1 word every 2 seconds), then have the patient repeat as many of the words as s/he can recall. Do this for 3 trials. After completing Trial 3, continue to Part B. Read each word and ask the patient to respond with "Yes" if the word was on the list or "No" if it was not.

After ALL Neurocognitive tests have been administered to the patient for this visit, ask the patient to recall the words you read to them at the beginning of the test. Mark the box next to each word the patient accurately recalls for each trial.

FREE RECALL & RECOGNITION: *Semantic Categories: Four-Legged Animals, Precious Stones, Human Dwellings*

1. PART A - FREE RECALL: For each trial, mark the box next to each word word the patient accurately recalls for each trial.

3. PART C - DELAYED RECALL

	Trial 1	Trial 2	Trial 3	Delayed Recall
LION	☐	☐	☐	☐
EMERALD	☐	☐	☐	☐
HORSE	☐	☐	☐	☐
TENT	☐	☐	☐	☐
SAPPHIRE	☐	☐	☐	☐
HOTEL	☐	☐	☐	☐
CAVE	☐	☐	☐	☐
OPAL	☐	☐	☐	☐
TIGER	☐	☐	☐	☐
PEARL	☐	☐	☐	☐
COW	☐	☐	☐	☐
HUT	☐	☐	☐	☐

2. PART B - RECOGNITION: "x" Yes or No beside each word to indicate the patient's response.

	Y	N		Y	N		Y	N		Y	N		Y	N		Y	N
HORSE	☐	☐	ruby*	☐	☐	CAVE	☐	☐	balloon	☐	☐	coffee	☐	☐	LION	☐	☐
house*	☐	☐	OPAL	☐	☐	TIGER	☐	☐	boat	☐	☐	scarf	☐	☐	PEARL	☐	☐
HUT	☐	☐	EMERALD	☐	☐	SAPPHIRE	☐	☐	dog*	☐	☐	apartment*	☐	☐	penny	☐	☐
TENT	☐	☐	mountain	☐	☐	cat*	☐	☐	HOTEL	☐	☐	COW	☐	☐	diamond*	☐	☐

4. Discontinued: Testing discontinued? ☐ Yes *(Complete the Neurocognitive Tests Discontinued/Not Done CRF)*
☐ No

Trail Making test: Part A

Procedure

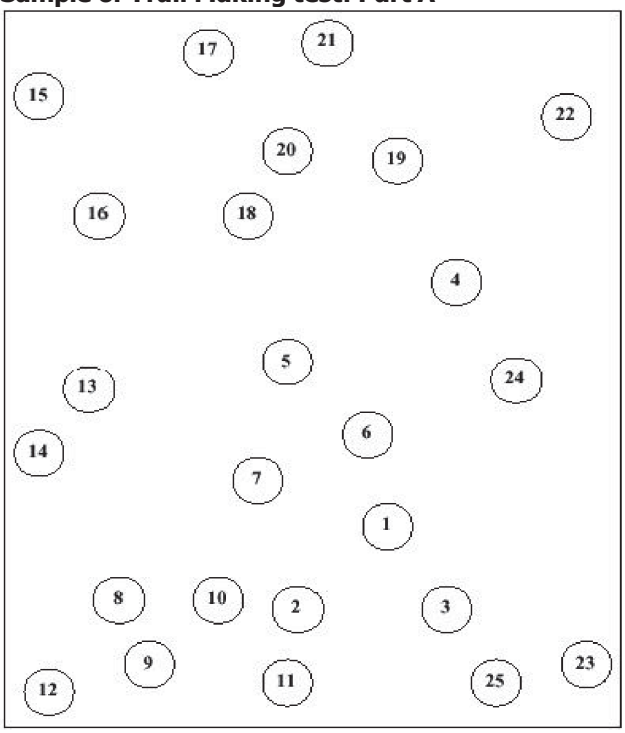
1) Position the participant at a table.
2) Place the practice sheet for part A flat on the table in front of them.
3) Provide the participant with a pen and explain the test to them showing the elements in the practice sheet. Ask the participant to draw a line between number 1 and number 2, then to draw a line between 2 and 3 and so on, in order, until reaching the end (number 8 in the practice sheet).
4) Ask the participant to not lift the pen from the paper.
5) Ask the participant to complete the practice test.
6) After successful completion of the practice test, show the participant the test sheet. Explain to the participant that on this page there are more numbers, but the procedure is the same.
7) Ask the participant to complete the test in the same way s/he completed the practice sheet. The participant must draw lines between numbers in numerical order starting from number 1 and finishing at number 25.
8) Ask the participant to draw the lines as fast as s/he can, but remind them not to lift the pen from the paper.
9) Start timing and continue timing the test even if the patient makes errors until s/he reaches the end (number 25).
10) If the participant makes an error, say "stop" and return the participant to his or her last correct response.
11) Stop timing when the participant reaches number 25 and record the time.

Trail Making test: Part B

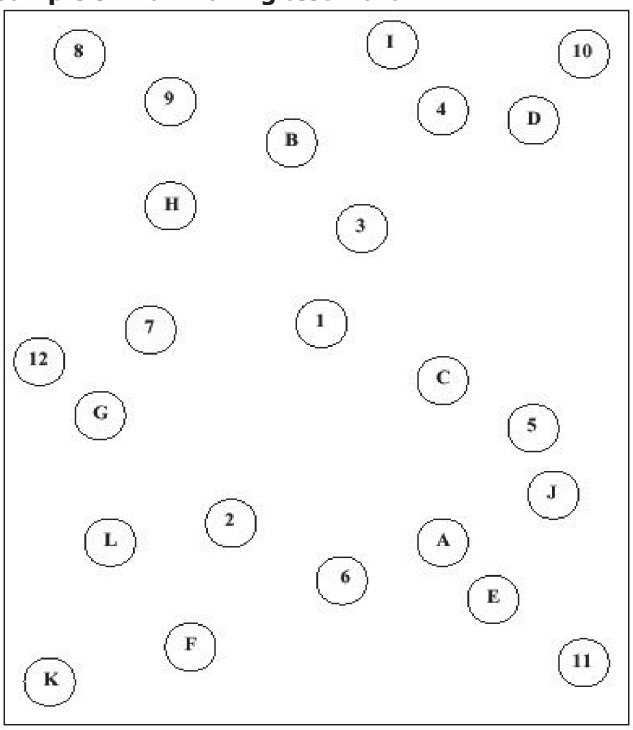
Procedure

1) Place the practice for part B on the table in front of the participant.
2) Explain to the participant that on this sheet there are some numbers and letters. The beginning of the task is again number 1. However, this time the participant must draw a line from number 1 to letter A, then a line between A and 2, followed by a line from 2 to letter B, then a line from B to 3 and from 3 to C and so on. The participant must continue alternating numbers and letters in ascending numerical and alphabetical order until reaching the end (letter D on the practice sheet).
3) After successfully completing the practice sheet, show the test sheet to the participant.
4) Again, explain to the participant that in this sheet there are more number and letters. Ask the participant to complete the test in the same way s/he completed the practice one.
5) Ask the participant to draw the lines as fast as s/he can, but remind them not to lift the pen from the paper until the test is completed.
6) Start timing and continue timing the test even if the participant makes errors until s/he reaches the end (letter L). As in part A, if the participant makes an error, return the participant to his or her last correct response.
7) Stop timing when the participant reaches letter L and record the time.

Sample of Trail Making test: Part A



Sample of Trail Making test: Part B



Grooved Pegboard test

The Grooved Pegboard (Lafayette Instruments) is a metal board (10 x 10 cm) with 25 holes arranged in 5 rows containing 5 holes each. Every hole on the board has a channel or groove randomly orientated in different directions. The kit also includes 25 metal round pegs with a key or ridge running longitudinally which must be placed in the holes. To do so, the participant needs to rotate the pegs to the correct position for insertion.

For the test, the examiner will ask the participant to insert all the 25 the pegs as fast as s/he can.

The participant must complete one row before starting a new one.

The test is timed, so the examiner will start timing when the participant is ready to begin the test and will stop timing only when the last peg is properly inserted. The test will be performed with each hand starting with the dominant one. Time to completion is scored separately for each hand.

Example of Grooved Pegboard:

EME
HS&DR
HTA
PGfAR
PHR

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