Title: Cost-effectiveness of protease inhibitor monotherapy versus standard triple-therapy in the long-term management of HIV patients: analysis using evidence from the PIVOT trial

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Manuscript category: original paper

Running head: Cost-effectiveness of PI monotherapy

Word count: 3989

Abstract

Background: Protease inhibitor monotherapy (PI-mono) can maintain virological suppression in the majority of patients once this has been established on triple therapy and may also have the potential for substantial cost savings arising from the use of fewer drugs. However, the cost-effectiveness of PI-mono has yet to be demonstrated.

Objectives: We examine the cost-effectiveness of protease inhibitor (PI) monotherapy with prompt return to combination therapy in the event of viral load rebound compared to ongoing triple therapy in patients with suppressed viral load on combination antiretroviral therapy in the United Kingdom.

Methods: The analysis used data from the PIVOT Trial in which HIV-positive adults with suppressed viral load for ≥24 weeks on combination antiretroviral therapy were randomised to maintain ongoing triple therapy or to a strategy of PI monotherapy with prompt return to combination therapy if viral load rebounded. A cost-effectiveness analysis including long-term modelling was conducted. Main outcomes included NHS costs and quality-adjusted life-years (QALY) with comparative results presented as incremental cost-effectiveness ratios.

Results: PI monotherapy was cost-saving as a result of large savings in antiretroviral therapy drug costs while being no less effective in terms of QALYs in the within-trial analysis and marginally less effective with lifetime modelling. In the base-case analysis over three years, the incremental total cost per patient was -£6,424.11 (95% confidence interval: -£7,418.84 to -£5,429.38) and incremental QALYs were 0.0051 (-0.0479 to 0.0582) resulting in PI monotherapy 'dominating' ongoing triple therapy. Multiple scenario analyses found that PI monotherapy was cost-saving with no marked differences in QALYs. Modelling of life-time costs and QALYs showed PI monotherapy was associated with significant cost-savings and was marginally less effective; with PI monotherapy being cost-effective at accepted cost-effectiveness thresholds in all but one scenario analysis.

Conclusions: Under most assumptions PI monotherapy appears to be a cost-effective treatment strategy compared to ongoing triple therapy for HIV-infected patients who have achieved sustained virological suppression.

Key Points for Decision Makers

- A strategy of PI monotherapy with prompt return to combination therapy in the event of viral load rebound appears to be cost-effective compared to ongoing triple therapy for HIV-1 infected patients who have achieved sustained virological suppression.
- This is as a result of the large cost-savings associated with PI monotherapy and minimal impacts on health outcomes.
- The financial resources freed-up by increased implementation of PI monotherapy could be reallocated to enhance other aspects of HIV care that are currently proving a challenge for resource-constrained HIV budgets, or improve health outcomes in other types of NHS patients.

INTRODUCTION

The current standard-of-care treatment for people living with human immunodeficiency virus (HIV) is combination antiretroviral therapy (ART), usually consisting of two nucleoside reverse transcriptase inhibitors (NRTI), combined with a third drug: either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) or an integrase inhibitor[1,2]. A number of relatively short-term trials, usually testing fixed drug choices in PI monotherapy and control regimens, have suggested that PI monotherapy may be able to maintain virological suppression once this has been established on triple therapy[3]. It has been suggested that this approach may also be cost-effective[4,5]. The PI monotherapy versus Ongoing Triple therapy (PIVOT) study is a recent pragmatic randomised trial that compared a strategy of PI monotherapy with prompt re-introduction of NRTIs for viral load rebound with standard of care triple therapy in patients who had achieved viral load suppression on triple therapy. The trial was designed to resemble routine clinical practice, with flexibility in the choice of drugs for both PI monotherapy and the standard of care arms, and with the larger numbers and longer term follow-up needed in order to judge the impact of this approach on more meaningful longer-term endpoints. The trial found PI monotherapy to be non-inferior to standard of care on the primary endpoint of loss of future drug options and that it did not change overall clinical outcomes or the frequency of toxicity. Therefore, PI monotherapy could be considered an acceptable treatment option for the long-term management of HIV infection[6].

One attraction of PI monotherapy may be the potential of substantial cost savings arising from the use of fewer drugs[4,5]. However, the higher frequency of viral load rebound seen in the PIVOT trial and some other trials and the consequent need for closer monitoring, as well as the requirement of a substantial proportion of patients to re-introduce combination therapy, may serve to reduce the overall cost savings from this strategy.

Cost-effectiveness analysis (CEA) is a tool used within the UK National Health Service (NHS) to prioritise health care resources to where they can be the most valuable, in terms of improving the health of different types of patients, with health measured in quality-adjusted life-years (QALYs). CEA requires a joint consideration of the costs of health care interventions, the health outcomes they produce and the effect on other patients' health if the system funds a more expensive intervention for a specific patient group which displaces other types of treatments because of the constrained budget. In CEA the latter 'opportunity costs' are reflected in the cost-effectiveness threshold which indicates how much additional cost needs to be imposed on the budget for one QALY to be forgone by other types of patient[7]. The aim of this analysis was to determine, using the PIVOT

trial data, the cost-effectiveness of PI monotherapy when applied to the long-term management of HIV in the routine clinical care setting.

METHODS

Overview

The methods we employed are consistent with those recommended by the National Institute for Health and Care Excellence (NICE)[8]. These include costs being considered from the perspective of the NHS , health outcomes being assessed using QALYs and costs and QALYs being discounted at an annual rate of 3.5%. For the base-case analysis a 3-year time-horizon was used (156 weeks).

Study population

Data for clinical outcomes, health-related quality of life (HRQoL) and resource use comes from the PIVOT trial. The PIVOT trial was conducted in 43 hospital based HIV treatment centres in the UK from November 2008 to November 2013. Full details of the PIVOT trial design, analysis and results can be found elsewhere[6]. Briefly, the trial enrolled 587 adult patients (23% female, 32% non-white ethnicity) who were taking stable combination ART with no change in the 12 weeks prior to screening, who had a VL < 50 copies/ml at and for at least 24 weeks before screening, and who had a CD4+ cell count >100 cells/mm^3 at screening. Participants were randomised to maintain ongoing triple therapy (OT, n=291; initially 54% on NNRTI and 46% on PI-containing regimen) or switch to a strategy of physician-selected ritonavir-boosted PI monotherapy (PI-mono, n = 296; initially 78% darunavir, 14% lopinavir) with prompt return to triple therapy in the event of VL rebound. Drug switches in both groups were allowed for toxicity, convenience and for VL failure. Participants were followed for up to 59 months (median follow-up 44 months)[6]. Retention rates were high with 2.7% withdrawn or lost to follow-up over the entire trial period.

Outcomes

A QALY is defined as a year lived in full health and it is the preferred outcome measure in economic evaluations as it captures the impact of treatment on both life expectancy and HRQoL[7]. To calculate the total QALYs gained per patient, the patient's length of life estimated from mortality data in PIVOT is weighted by their HRQoL. The latter was measured in PIVOT using the three-level version of the EuroQol five dimensions of health questionnaire (EQ-5D-3L)[9]. Measurements were taken at baseline and at the scheduled follow-up

visits every 12 weeks. The EQ-5D-3L responses were converted into the EQ-5D index score using weights based on the UK public preferences where a score of 1 represents full health, 0 accords with death and negative values (HRQoL considered worse than death) are possible[10].

Resource use and costs

Data on resource use were collected in PIVOT at scheduled study visits (protocol mandated every 12 weeks in both arms, with additional visits at week 4 and week 8 in the PI-mono arm). The use of the following types of resources was recorded: ART use, HIV clinic visits, visits to accident and emergency (A&E), non-HIV outpatient clinics, GP visits, hospital inpatient stays and the use of concomitant drugs. Measurement of PI drug concentration was performed at 4 weeks in all patients in the PI-mono arm as mandated in the protocol; any subsequent drug concentration measurements were ignored. All reported visits to GPs, A&E departments, non-HIV outpatient clinics and hospital admissions were included. HIV clinic visits were divided into those that would likely be required for routine clinical management and those that were in excess of that, arising from additional protocol requirements (non-routine HIV clinic visits). In the base-case analysis, the costs of all visits in both groups were included in the calculations. As such, the base-case also includes resource use that could be considered mainly attributable to the trial protocol, and this is considered further in scenario analysis.

Unit costs in 2012 prices (see Table 1) were obtained from routinely published national cost sources: the British National Formulary[11], the Department of Health's Commercial Medicines Unit's Electronic Market Information Tool[12], the Personal Social Services Research Units report on Unit Costs of Health and Social Care[13] and the National Health Service reference costs[14].

Analysis

Cost-effectiveness was based on differential mean costs and QALYs between the two forms of management. If the more effective management was also the more costly, an incremental cost-effectiveness ratio (ICER) was calculated as the ratio of differential mean costs and differential mean QALYs, which gives the cost per additional QALY gained [7]. To assess value for money, estimated ICERs are compared to the cost-effectiveness thresholds of £20,000 to £30,000 per QALY used by NICE [8], and a recent estimated threshold using UK data to estimate the cost per QALY generated by the NHS at the margin (£12,936 per QALY)(15), an attempt to estimate what health can be generated or is displaced with cost savings or cost increases respectively. Estimates of resource use, costs and QALYs were also calculated.

All statistical analyses were conducted using Stata version 12.1 (StataCorp, College Station, TX, USA). Multiple imputation (MI) was used to handle missing data on costs and outcomes, although a scenario analysis examining only patients with complete data was also considered[16–20]. Estimates of resource use are presented based on complete case data only to avoid problems with imputing larger number of variables (i.e. only patients with no missing data points are included)[20]. Generalised linear regression-models (GLMs) were used to obtain the incremental estimates of costs and QALYs whilst adjusting for any imbalances in baseline characteristics (with the latter selected *a priori*)[21]. Costs and QALYs were adjusted for the following baseline covariates: age, gender, ethnicity, time since HIV diagnosis, history of diabetes, smoking status, history of coronary artery disease, and CD4+ cell count; for QALYs baseline EQ-5D was also included [22].

Uncertainty in cost-effectiveness was assessed using probabilistic sensitivity analysis (PSA) and the probability of cost-effectiveness at different cost-effectiveness thresholds was calculated[23,24] .To conduct the PSA, the variance-covariance matrices from the cost and QALY regressions were extracted and the corresponding Cholesky decompositions calculated to parameterise a multivariate normal distribution from which 1000 simulated random draws of incremental mean costs and QALYs were estimated. Scenario analyses were conducted to explore other uncertainties including (i) an analysis using lower prices of ARTs to reflect availability of generics (with a 10% reduction in the price of ARTs in the PI-mono group and 30% in the OT group to reflect that PI-mono treatments are more likely to still be under patent and are also more expensive to manufacture); (ii) an analysis with exclusion of costs considered to be protocol-driven (the week 8 visit in the PI-mono arm, alternate 12 weekly visits in the OT arm, the PI concentration measurement in the PI-mono arm, and the neurocognitive testing in both arms); (iii) a complete case analysis including only patients that have no missing data points; (iv) an analysis that excluded patients who died within three years of randomisation – as the number of deaths was greater in PI-mono group, considered most likely a chance finding, unrelated to treatment allocation [6].

Secondary analyses explore the implications of varying the base-case assumption that no differences in costs or QALYs between the treatment groups persist beyond the trial follow-up period. Two scenarios were considered. Firstly, a 'return to standard of care' scenario which assumes that all PI-mono patients switch back to combination therapy after three years and that there is no difference in mortality between the alternative forms of management (i.e. mortality was equivalent in the trial and survival curves were assumed parallel following the end of trial). The mean total cost per year in the OT group during the trial was applied to both

groups annually after the end of the trial until death for each patient. A second 'maintain treatment strategy' scenario assumes that all patients stay on the treatment they were receiving at 3 years and that any difference in mortality by that point would continue into the long-term (a hazard ratio for all-cause mortality of 3.3 (95% confidence interval, 0.38 to 28.91) was applied to obtain life-expectancy for PI-mono patients)[6]. Costs per patient during the third year of the trial were used as the subsequent annual cost of treatment until death for each patient for this scenario.

For both scenarios, the patient-specific life-expectancies were calculated using a predictive model from the UK collaborative HIV cohort (UK CHIC) study [25,26] and data on mortality in the UK general population from the Office of National Statistics[27]. Life expectancy was estimated conditional on CD4+ cell count based on the CD4+ cell count closest to final three years follow-up visit[25]. Long-term HRQoL was based on taking each patient's EQ-5D index score at the final three year follow-up visit in PIVOT together with an annual decrement of 0.00029 applied to reflect lower HRQoL with age[28].

RESULTS

Resource use, costs and QALYs

Resource consumption within three years is presented for the complete case patients in Table 1. After three years of follow-up, 39.1% of patients in the PI-mono arm had returned to triple therapy, with 60.9% remaining on mono-therapy. PI-mono patients had on average 17.0 total HIV clinic visits compared to 15.0 total visits for OT patients. However, when HIV clinic visits that were considered to be protocol-driven (i.e. non-routine HIV clinic visits, likely to be in excess of those required for routine clinical management) were excluded, PI-mono patients had on average 16.6 routine HIV clinic visits compared to 8.3 visits for OT patients reflecting the increased monitoring that may be required for patients in the PI-mono arm. Other resource use was broadly similar across arms.

Unadjusted costs (not taking into account baseline differences) over three years based on the imputed data are presented in Table 2. ART costs were lower in the PI-mono arm (£14,335.31 compared to £21,954.84) and routine HIV clinic visit costs were higher (£6,648.38 compared to £3,359.13). Protocol driven costs were higher in the OT arm (£2,676.92 compared to £573.32). Other costs were broadly similar across the arms, resulting in total costs being markedly lower in the PI-mono arm (£22,924.74 compared to £29,323.46).

Unadjusted QALYs (not taking into account baseline differences) based on the imputed data are presented in Table 2. Unadjusted QALYs were marginally lower in the PI-mono arm than the OT arm (2.445048 QALYs compared to 2.467436 QALYs respectively).

Base-case cost-effectiveness

Cost-effectiveness results are presented in Table 3. In the base-case analysis, after adjusting for baseline patient covariates, PI-mono was a dominant strategy compared to OT i.e. it offered both cost-savings and a small QALY gain. The adjusted incremental total mean cost of PI-mono per patient was -£6,424.11 (95% confidence interval: -£7,418.84 to -£5,429.38) over a three year period. The cost-savings in the PI-mono group were mainly attributable to the saving in ART drug costs. Adjusted estimates of differential QALYs showed that PI-mono patients gained an average of 0.0051 QALYs (95% confidence interval: -0.0479 to 0.0582) compared to OT patients. The PSA revealed that PI-mono was cost-effective in 100% of simulations regardless of whether a £12,936/QALY, £20,000/QALY or a £30,000 per QALY cost-effectiveness threshold was applied.

Scenario analysis

Scenarios reducing the price of ARTs to allow for the introduction of generic products and excluding the costs of visits and tests likely required only for the trial protocol resulted in greater cost reductions in the OT arm and, therefore, reduced cost savings associated with PI-mono. However, PI-mono still appeared highly cost-effective. In the complete case analysis, PI-mono remained cost-saving but resulted in a reduction in mean QALYs compared to OT. However, PI-mono remained the preferred option based on cost-effectiveness as the mean QALY loss was small (with an increment of only -0.0227; 95% confidence interval: -0.0878; 0.0424) and the large cost-savings were preserved. The resulting ICER of OT compared to PI-mono was £282,641 per additional QALY, which is markedly higher than accepted cost-effectiveness thresholds. In the scenario excluding mortality, there were higher mean QALYs with PI-mono, which remained dominant as in the base-case.

In both extrapolation scenarios, PI-mono was found to be cost-saving but less effective compared to OT. In the "return to standard of care" scenario (no deaths, all on triple ART beyond three years), PI-mono remained the cost-effective strategy at accepted cost-effectiveness thresholds as the large cost savings outweighed the small health loss. In the 'maintain treatment strategy' scenario (death rate continues as observed in trial and patients continue on same treatment beyond three years), PI-mono remained the cost-effective strategy at cost-

effectiveness thresholds of £12,936 per QALY and £20,000 per QALY, but not at £30,000 per QALY, with OT having an ICER of £20,722 per QALY compared to PI-mono.

DISCUSSION

PI-mono was shown to be cost-effective compared to OT for HIV-1 infected patients under all assumptions examined, with the possible exception of the 'maintain treatment strategy' life-time projection scenario using the upper range of NICE's cost-effectiveness threshold of £30,000 (even in this scenario, PI-mono was still cost-effective at the two lower thresholds). The cost-effectiveness of PI-mono compared to OT is mainly explained by the substantial cost savings due to reduced use of ART drugs in PI-mono, with minimal difference in outcomes between groups. Although consideration of cost savings is rarely the primary reason for choosing a particular ART regimen or treatment strategy, the financial resources freed-up by increased implementation of PI-mono could be reallocated to enhance other aspects of HIV care that are currently proving a challenge for resource-constrained HIV budgets, such as the provision of direct acting antiviral agents for HCV (which are effective but extremely expensive)[29] or the provision of ART to patients at higher CD4 T-cell counts as supported by the recent findings of the START trial[30]. However, before resources are reallocated to other areas of HIV care these should also be assessed to ensure they represent a cost-effective use of resources. Cost savings could also be used to enhance patient outcomes for other types of patients. Based on recent research on the marginal cost of generating health outcomes in the NHS[15] and assuming this research results in 45,000 patients being switched from OT to PI-mono[31], the base case estimates of the cost savings from PI-mono could be used to generate 22,354 QALYs in other NHS patients including 1,486 lives prolonged and 6,735 life years gained. It has been argued that a higher cost-effectiveness should be used when an intervention results in cost savings but lower health outcomes[32]. However, for health systems with constrained expenditures, the cost-effectiveness threshold represents the opportunity cost in terms of health which would be lost (or could be generated) if extra resources are required (or released) by the introduction of a new health care intervention. This is the conceptualisation embodied in NICE's methods guidelines[8], the underlying premise being that the purpose of the health care system is to maximise the amount of health benefits delivered to patients. If PI monotherapy could be introduced and more health generated elsewhere with the released resources, then this would be of benefit to the system. Recent empirical evidence from the UK used marginal changes in spend, both positive and negative, to estimate the cost-effectiveness threshold[15]. As such the same threshold should be used whether an intervention results in increased or decreased costs.

Two previous studies have investigated ART drug costs following the introduction of PI-based mono-therapy and compared it to the ART drug costs of triple therapy[4,5]. Restelli et al.[4] estimated that the incremental

cost of PI monotherapy compared to combination therapy would be -€3,382 per year (a cost saving of approximately £8,000 over a three year period). Gazzard et al.[5], in an analysis based on data from the MONET Trial of darunavir monotherapy[27] estimated annual cost-savings on ART drugs of £4,126, i.e. £12,378 in three years based on UK drug prices (no other costs were included in the analaysis). Both studies provide similar results to the base-case analysis here, where cost savings were estimated to be £6,424 per patient over three years. Neither of these previous studies considered the impact of PI monotherapy on health outcomes as measured by QALYs.

The PIVOT trial protocol mandated 12-weekly visits for patients in both treatment arms throughout follow-up, with 2 additional early visits in the PI-mono arm. However, patients who are stable on combination therapy may be seen less frequently than this in routine clinical care, typically every 6 months in some centres. In the scenario where we reduced the combination therapy visits to 6 monthly (by discounting the costs associated with additional protocol-mandated visits in excess of this frequency), the estimated cost-saving of PI-mono fell to £4,307 over a three year period. However, the PIVOT trial also found that the risk of VL rebound on PI-mono was much reduced after the first year (25 per 100 person years in the first year versus 6 per 100 person years thereafter) suggesting that a decrease in the intensity of follow-up visits may also be possible for patients who have been established on PI monotherapy for at least a year with sustained VL suppression. The strategy used in the PIVOT trial of repeating VL testing on the same sample in the event of a first detectable VL may also help to decrease the number of clinic visits and therefore the costs of monitoring. Lastly, many treatment centres in the UK now have systems in place for monitoring VL in the community in order to minimise visits to specialist centres for blood taking or for discussion of (satisfactory) results with a clinician. Thus the additional requirements for expensive specialist centre visits for monitoring PI monotherapy may be relatively modest and the associated impact on the cost savings resulting from PI monotherapy are likely to be less than under the conservative assumptions used in our scenario.

This research is subject to a number of uncertainties. The cost-effectiveness results presented are conditional on the current ART prices. A number of first-line ART drugs are coming off patent, new options for first line therapy with new classes of drugs (particularly integrase inhibitors) are driving down drug costs, and evidence indicates that a reduction in the dose of efavirenz (the most commonly used NNRTI drug in the UK) may also be possible without loss of efficacy[34]. 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,

thereby limiting its cost-saving potential. In the scenario exploring the impact of a 30% reduction in ART drug costs for the OT group and a 10% reduction in the PI-mono group, PI-mono remained cost-effective. Nonetheless, future ART prices will have important implications for how the results of the study are used to guide practice. Secondly, the longer-term modelling is subject to considerable uncertainty as costs and outcomes are extrapolated beyond what was observed in the PIVOT trial data, although the scenarios we have explored indicate that cost-effectiveness is likely to be preserved in longer-term follow-up (especially as the frequency of VL rebounds diminishes in later follow up, as discussed above). Thirdly, the potential adverse influence of protease inhibitors on liver function may impact on the generalisability of the PI monotherapy treatment strategy. In the trial population, which would likely be typical of the patients selected for monotherapy, the incidence of hepatitis (laboratory grade 3 or 4) was only 1% in the PI monotherapy arm (same in the OT group) over a median of 44 months[6], so this is unlikely to impact the cost effectiveness results. The trial excluded patients with active or planned Hepatitis C treatment and ordinarily such patients would not be selected for treatment with PI monotherapy. This may affect the overall generalisability of the treatment strategy and potential cost savings in some settings where the HCV co-infection rates are very high. Fourthly, this study has used the EQ-5D instrument to measure the HRQoL of patients. This is the recommended instrument in the UK for all diseases[8], has been used in recent HIV analyses in the UK[35] and has been shown to be a useful measure in patients with HIV[36]. However, other HRQoL measures exist and could alternatively be used. Fifthly, extrapolation beyond the trial is challenging and the extrapolation scenarios were selected as a pragmatic way to represent the possible extremes of the impact of extrapolating the results over the patients' lifetimes. Whilst neither of these may be considered realistic we hope that they are informative by representing the bounds of what could be expected. Finally, it is possible that there are other aspects of routine care that may not have been reflected by the trial and that may have an influence on the cost-effectiveness analyses. However, this is expected to be minor given that the PIVOT trial was conducted at 43 HIV treatment centres across the UK (including all of the major treatment centres and a range of smaller treatment centres), had relatively good representation of the major high HIV prevalence demographic groups in the UK, and was designed as a pragmatic trial allowing flexibility for the clinician to select and change ART drugs (in both treatment arms, as long as within the treatment strategy) and therefore should be representative of routine clinical practice.

Conclusions

Under most assumptions, a strategy of PI-mono with prompt return to combination therapy in the event of VL rebound appears to be cost-effective compared to OT for HIV-1 infected patients who have achieved sustained virological suppression on highly-active ART as a result of large cost-savings and minimal impact on health outcomes.

ACKNOWLEDGEMENTS

We thank all the patients and staff from all the centres participating in the PIVOT trial, and the UK Community Advisory Board and African Eye for community support.

Author contributions: DD, NP and MS designed the study. WS, AA-P, DD and NP contributed to the coordination and oversight of the study. LO, SW and MS conducted the health economics analysis. All authors participated in data interpretation. The manuscript was drafted by LO, SW and MS and all authors provided input into the report and approved the final version of the manuscript.

Compliance with Ethical Standards

Ethics committee: The protocol was approved by the Cambridgeshire 4 Research Ethics Committee and Medicines and Healthcare Products Regulatory Agency and has been performed in accordance with the ethical standards of the Declaration of Helsinki.

All participants provided written informed consent.

Conflicts of interest: LO reports funding from the North Denmark Region and Aalborg University and has worked as a paid consultant for Novartis Healthcare ; SW reports grants from NIHR HTA programme, during the conduct of the study; WS reports grants from NIHR HTA programme, during the conduct of the study; AA-P reports non-financial support from UK Clinical Research Network, during the conduct of the study; grants from Janssen, grants from ViiV, outside the submitted work; DD reports grants from NIHR HTA programme, during the conduct of the study; NP reports grants from National Institute of Health Research (NIHR) HTA programme, during the conduct of the study; grants, personal fees and non-financial support from AbbVie, personal fees and non-financial support from Merck, grants, personal fees and non-financial support from Janssen, personal fees and non-financial support from Roche, grants and non-financial support from GSK, non-financial support from Gilead, outside the submitted work; MS reports grants from NIHR HTA programme, during the conduct of the study and consultancy fees from Gilead.

Source of support: PIVOT was funded by the National Institute for Health Research Health Technology Assessment programme (project number 06/403/90). The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health.

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Tables

Table 1: Use of healthcare resources within three years follow-up for complete cases

Resource type	PI-mono (n=266)			OT (n=254)			Unit cost [Source]
	Mean per patient (SD)	Median per patient (IQR)	Used by n (%)	Mean per patient (SD)	Median per patient (IQR)	Used by n (%)	
ART drug use by the three year follow-up visit							
Mono-therapy			162 (60.9)			4 (1.6)	Various [11,12]
Any triple-therapy use			104 (39.1)			250 (98.4)	Various [11,12]
No use			0 (0)			0 (0)	£0
HIV clinics							
HIV clinic visits	16.60 (3.74)	15 (4)	266 (100)	8.31 (3.9)	7 (3)	254 (100)	PI Mono: £411.81 [14][PC] OT: £404 [14]
Primary care							
GP visits	6.24 (6.16)	5 (7)	244 (91.7)	6.06 (6.06)	4.75 (6)	234 (92.1)	£53 [13]
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 [14]
Inpatient admissions	0.368 (0.83)	0 (0)	60 (22.6)	0.311 (0.79)	0 (0)	50 (19.7)	Various [14]
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 [13,28–30]
PI drug concentration measurements	0.974 (0.16)	1 (0)	259 (97.4)	0 (0)	0 (0)	0 (0)	£60 [PC]
Non routine HIV-clinic visits	0.98 (0.24)	1 (0)	255 (95.9)	6.69 (0.67)	7 (0)	254 (100)	PI-Mono: £411.81 [14][PC] OT: £404 [14]
Concomitant drug use at the three year follow-up visit							
Cholesterol lowering agents			59 (22.2)			35 (13.8)	Various [11]

A&E - Accident and emergency; ART – antiretroviral therapy; GP – general practitioner; IQR - Interquartile range; OT – ongoing triple therapy; PC – personal communication; PI – protease inhibitor; PI-mono – protease inhibitor monotherapy; SD – standard deviation. The phrase "Various" indicates that several unit costs were used and rather than listing them all the source, from which they were all drawn, is presented.

Table 2: Unadjusted costs by category and QALYs accrued within three years

Costs				
Cost category	**Protease Inhibitor monotherapy** (n=296 , m=20)		**Ongoing triple therapy** (n=291 , m=20)	
	Mean (SE)	% of Total	Mean (SE)	% of Total
ART	£14,335.31 (286.52)	62.5	£21,954.84 (255.39)	74.9
Routine HIV clinic visits	£6,648.38 (100.08)	29.0	£3,359.13 (112.04)	11.5
Primary care	£325.52 (19.15)	1.4	£316.26 (21.24)	1.1
Hospital services	£1,010.49 (120.40)	4.4	£988.46 (126.55)	3.4
Trial protocol driven	£574.32 (6.82)	2.5	£2,676.92 (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
QALYs	Mean (SE)		Mean (SE)	
Total	2.445048 (0.0335)		2.467436 (0.0327)	

n=number of patients, m=number of imputed data sets, SE=standard error, ART=Antiretroviral therapy, QALY=Quality-adjusted life-year

Table 3: Cost-effectiveness results

Analysis	Incremental cost [PI-mono – OT] (95% CI)	Incremental QALY [PI-mono – OT] (95% CI)	ICER £ per QALY	Probability of being cost-effective at thresholds of £20,000/QALY (£30,000/QALY) {12,936/QALY}
Base-case analysis				
Base-case	-£6,424.11 [a] (-£7,418.84; -£5,429.38)	0.0051 [a] (-0.0479; 0.0582)	PI-mono Dominant	100% (100%) {100%}
Alternative scenarios				
Reduced ART drug prices	- £1,279.97 [a] (-£2,134.85; -£425.08)	0.0051 [a] (-0.0479; 0.0582)	PI-mono Dominant	97.47% (93.84%) {99.03%}
Trial protocol costs excluded	- £4,307.27 [a] (-£5,285.24; -£3,329.31)	0.0051 [a] (-0.0479; 0.0582)	PI-mono Dominant	100% (100%) {100%}
Complete case analysis	- £6,417.15 [b] (-£7,393.62; -£5,440.68)	-0.0227 [c] (-0.0878; 0.0424)	282,641*	100% (100%) {100%}
Mortality excluded	- £6,406.41 [d] (-£7,374.08; -£5,438.74)	0.0197 [d] (-0.0291; 0.0685)	PI-mono Dominant	100% (100%) {100%}
Modelling of life-time cost-effectiveness				
'Return to standard of care' scenario	-£38,248 [d] (-£46,081; -£30,416)	-0.3884 [d] (-1.1299; 0.3531)	98,475*	99.98% (98.52%) {100%}
'Maintain treatment strategy' scenario	-£69,065 [d] (-£76,212; -£61,919)	-3.2597 [d] (-3.8945; -2.6249)	20,772*	63.31% (0.19%) {100%}

CI – Confidence interval; ICER – Incremental cost-effectiveness ratio; NNRTI – Non-nucleoside reverse transcriptase inhibitor; OT – ongoing triple therapy; PI – protease inhibitor; PI-mono – protease inhibitor monotherapy; QALY – quality adjusted life-year; *the ICER of OT compared to PI-mono; [a]PI-mono (n=296, m=20) & OT (n=291, m=20); [b]PI-mono (n=266, m=0) & OT (n=254, m=0); [c]PI-mono (n=142, m=0) & OT (n=130, m=0); [d]PI-mono (n=291, m=20) & OT (n=290, m=20)