Poster # 550LB

Randomised Controlled Trial of a PI Monotherapy Switch Strategy for Long-term HIV Management (The PIVOT Trial)

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Background

Previous randomised trials show patients switching to PI monotherapy maintain high rates of viral load (VL) suppression over 48-96 weeks, sometimes meeting VL non-inferiority criteria. However, longer-term resistance and toxicity risks are uncertain and the place of PI monotherapy in clinical management of HIV therefore remains controversial. We designed a pragmatic trial, conducted in routine clinical care settings in the UK, which set out to determine the impact of PI monotherapy on meaningful long-term outcomes.

Methodology

The Protease Inhibitor Monotherapy Versus Ongoing Triple Therapy (PIVOT) Trial was a 5-year prospective, randomised, controlled, open-label strategy trial performed in 43 centres in the United Kingdom. Ethics & regulatory approvals: Cambridgeshire 4 REC & MHRA.
Trial registration: ISRCTN-04857074.

Main inclusion criteria:

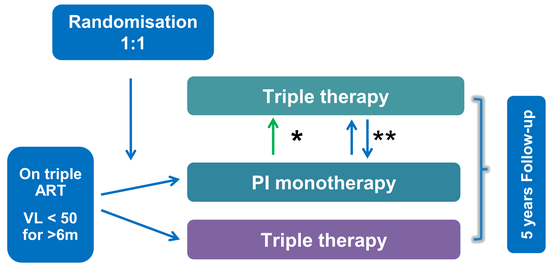
- HIV-positive adults
- Taking a stable NNRTI or PI-based regimen for at least 24 weeks with no change in the previous 12 weeks
- VL<50 copies/ml for at least 24 weeks before screening
- CD4 count > 100 cells/mm^3 at screening

Main exclusion criteria:

- Known major PI resistance mutation(s) on prior resistance testing (if performed, not mandated)
- Previous ART change for unsatisfactory virological response (change for toxicity prevention/management or convenience permitted)
- PI allergy or concomitant medication with PI interactions
- Pregnancy, history of cardiovascular disease, 10 year absolute coronary heart disease risk of >30%, insulin-dependent diabetes mellitus, active/planned hepatitis C virus treatment, or hepatitis B virus surface antigen positive.

Methodology (cont.)

Figure 1: Summary of trial design



Patients were randomised to maintain ongoing triple therapy (OTT) or switch to a PI monotherapy strategy (PIm) using a ritonavir-boosted PI (physician drug choice) with prompt re-introduction of NRTIs if unable to maintain VL suppression <50 copies/ml. VL was measured every 12 weeks, with resistance testing for all confirmed VL rebound (≥50 copies/ml × 3, including 1 re-test of same sample).

Primary outcome: *loss of future drug options*, defined as new intermediate/high level resistance to ≥1 drug to which the patient's virus was considered to be sensitive at trial entry

Secondary outcomes: included serious disease complications (AIDS, serious non-AIDS, all-cause death), total grade 3/4 adverse events and neurocognitive function change (annual 5-test battery).

Analysis: all analyses done as ITT. Tested hypothesis of non-inferiority of PIm on the primary outcome, margin 10%.

Results

We randomised 587 patients who were followed for a median (maximum) of 44 (59) months; 2.7% withdrew or were lost-to follow up (Fig 2). Baseline characteristics were well balanced between treatment arms (Table1). In PIm, 80% selected DRV/r, 14% LPV/r, 7% other PI/r at randomisation.

Results (cont.)

Figure 2 : CONSORT diagram

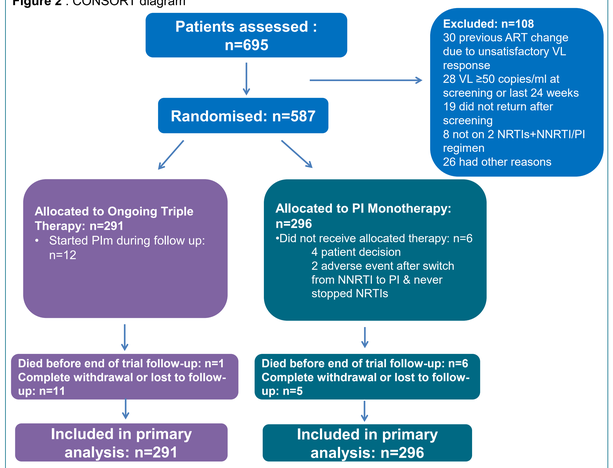


Table 1: baseline characteristics

Characteristic	OTT (n=291)	PIm (n=296)	Overall
Age (years)*	43 (37-49)	45 (39-50)	44 (38-49)
Mode of infection			
MSM	175 (60%)	176 (60%)	351 (60%)
Heterosexual	108 (37%)	108 (36%)	216 (37%)
Other	8 (3%)	12 (2%)	17 (3%)
Female	64 (22%)	73 (25%)	137 (23%)
Ethnicity			
White	206 (71%)	195 (66%)	401 (68%)
Black	73 (25%)	90 (30%)	163 (28%)
Other	12 (4%)	11 (4%)	23 (4%)
HCV infected (Ab +ve)	7 (2%)	14(5%)	21 (4%)
Baseline CD4*	512 (386, 658)	516 (402, 713)	513 (392, 682)
CD4 nadir*	181 (90,258)	170 (80, 239)	178 (86, 250)
Years since ART start*	3.9 (2.0,6.4)	4.2 (2.4, 6.9)	4.0 (2.2, 6.7)
No. drugs ever received *	5 (3,6)	4 (3,6)	4 (3,6)
PI or NNRTI at entry			
PI	134 (46%)	139 (47%)	273 (47%)
NNRTI	127 (54%)	155 (53%)	314 (53%)

VL rebound was much more common in PIm (Table 2), but all rebounds on PIm re-suppressed either spontaneously or with NRTI reintroduction. Sequences were obtained in 83% of confirmed VL rebounds. Few new resistance mutations were seen in either arm (Table 2) and of those observed, most appeared to have been archived prior to PIVOT entry.

Results (cont.)

PIm was non-inferior on the primary outcome of loss of future drug options and had fewer Grade 3/4 adverse events. There were no significant differences in serious disease complications or neurocognitive function between the arms. 58% in PIm remained on monotherapy at the end of trial and overall drug costs were substantially lower in this arm (Table 2).

Table 2: Number of patients with event, mean change in CD4 count or neurocognitive function, and mean costs - all during period from baseline to end of follow up.

Characteristic	OTT (n=291)	PIm (n=296)	Difference PIm–OTT (95% CI)	p-value
VL rebound ≥ 50 copies/ml, confirmed - n (%) [1]	8 (3.2%)	95(35.0 %)	31.8% (24.6 to 39.0%)	<0.001
Loss of future drug options [by 36 months] - n (%) [2]	2 (0.7%)	6 (2.1%)	1.4% (-0.4 to 3.4%)	0.15
Loss of future drug options [by end of trial] - n (%) [2]	4 (1.8%)	6 (2.1%)	0.2% (-2.5 to 2.6%)	0.85
By drug class – n				
NRTI	3	1	-	-
NNRTI	3	2	-	-
PI	1	3	-	-
CD4 change, cells/mm^3 mean (SE) [3]	+91 (9)	+108 (9)	+17 (-10 to +43)	0.21
Serious disease complication n (%)	8 (2.8%)	15 (5.1%)	2.3% (-0.8% to 5.4%)	0.15
Grade 3/4 adverse event n (%) [5]	159 (55%)	137 (46%)	-8.4% (-16.4% to 0.3%)	0.043
Neurocognitive function [NPZ-5] change -mean (SE)[3]	+0.51 (0.04)	+0.50 (0.04)	-0.01 (-0.11 to +0.09)	0.86
Cost of ART drugs, £ mean (SE)[4]	30,230 (860)	21,260 (700)	-8970 (-6,790 to -11,160)	–

Notes: [1]Kaplan-Meier estimates; [2]Kaplan-Meier estimates with bootstrap confidence interval for difference; [3]change to last measurement adjusted for baseline value; [4]standard UK formulary price, individual drugs; [5]Changed from figures in late-breaker abstract due to inclusion of more complete laboratory event data.

Conclusions

PI monotherapy, with prompt reintroduction of NRTIs for VL rebound, was a successful long-term management strategy, preserved future treatment options, was safe and well tolerated, and may be considered for more widespread use in long-term HIV care.

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