THE LANCET HIV

# Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Paton NI, Stöhr W, Arenas-Pinto A, et al. Protease inhibitor monotherapy for long-term management of HIV infection: a randomised, controlled, open-label, non-inferiority trial. *Lancet HIV* 2015; published online Sept 15. http://dx.doi.org/10.1016/S2352-3018(15)00176-9.

**SUPPLEMENTARY MATERIALS**

# Randomised controlled trial of a protease inhibitor monotherapy strategy for the long-term management of HIV infection

Paton NI, Stöhr W, Arenas-Pinto et al.

**SUPPLEMENTARY TABLE 1: Resistance test results in cases meeting the definition of the primary endpoint, loss of future drug options***

| Patient | Cumulative ART exposure before trial entry | | Time of resistance test (trial week)† | Cumulative ART exposure during trial ‡ | | Viral load (c/ml) at time of resistance test | Drug-resistance mutations present§ | | Drugs with reduced susceptibility¶ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 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) | 4,100 | 118I, 179D | - | - | - | - |
| 2 | d4T, TDF, EFV, FTC | DRV | -286 | - | - | - | - | 71V | - | - | - |
| | | | 193 | TDF, FTC, RPV | (DRV) | 1,500 | 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) | 5,400 | 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 | SQV, LPV | -179 | | | | - | - | - | - | - |
| | | | 51 | TDF, FTC | DRV | 2,300 | 106A | - | - | NVP[H], EFV[I] | - |
| **PI-mono group** | | | | | | | | | | | |
| 5. | FTC, TDF, EFV | - | -165 | - | - | - | - | 71T | - | - | - |
| | | | 48 | - | ATV | 23,400 | - | 20T, 50L/I,71T | - | - | ATV[H] |
| | | | 57 | - | ATV | 3,300 | - | 20T, 71T | - | - | - |
| | | | 61 | - | ATV | 2,400 | - | 71T | - | - | - |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 6. | ZDV, 3TC, ABC, EFV | LPV | 155 | - | DRV | 200 | - | 90M | - | - | SQV[I] |
| 7. | FTC, TDF, EFV | - | 73 | - | DRV | 300 | - | 71T, 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 | 1,100 | 103N | - | | NVP[H], EFV[H] | - |
| 10. | ZDV,3TC | LPV | 17 | - | DRV | 300 | 41L,215D | - | ZDV[I] | - | - |

* Drugs used for less than 28 days are not reported. ART, antiretroviral therapy; ABC, abacavir; d4T, stavudine; 3TC, lamivudine; FTC, emtricitabine; TDF, tenofovir; ZDV, zidovudine; SQV, saquinavir; FPV fosamprenavir; TPV tipranavir; ATV, atazanavir; NVP nevirapine; EFV , efavirenz; ETV etravirine; RPV, rilpivirine; RAL, raltegravir

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

‡ 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.

§ Drug resistance mutations limited to those used in the Stanford algorithm.

¶ Drug susceptibility determined from Stanford algorithm. List limited to drugs that are included as treatment options in British HIV Association 2012 treatment guidelines, with the addition of saquinavir. Superscript denotes level of predicted resistance: I=intermediate, H = high

**Supplementary Table 2: Causes of death, risk factors and HIV disease status during trial follow-up prior to the presentation of the terminal condition**

| Patient no. (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) | 58y male; 40 pack-year history of smoking; presented with right thigh mass; mediastinal and adrenal mass on CT | CD4 525 at baseline; VL suppressed from randomisation to presentation of terminal condition |
| 2. (PI-mono) | Trauma, presumed suicide (week 17) | 47y male; no history of depression | CD4 215 at baseline; VL suppressed from randomisation to death |
| 3. (PI-mono) | Pulmonary embolism (week 51) | 40y female; non-smoker; hospitalisation for encephalitis (week 40 to 50); pulmonary embolism secondary to deep venous thrombosis | CD4 333 at baseline; VL rebound week 36 due to non-adherence; re-suppressed partially with re-introduction of combination therapy |
| 4. (PI-mono) | Breast carcinoma, recurrent (week 7) | 54y female; non-smoker; angiosarcoma of breast 2y before study entry treated by mastectomy; | CD4 550 at baseline; VL supressed from randomisation to presentation of terminal condition |
| 5. (PI-mono) | Small-cell lung carcinoma (week 178) | 59y male: smoker for 30 years; presented with headache; CT lung mass, biopsy showed small cell carcinoma of lung | CD4 208 at baseline: VL suppressed from randomisation to presentation of terminal condition |
| 6. (PI-mono) | Glioblastoma (week 66) | 61y male; non-smoker; presented with headache at week 66; mass on CT head, biopsy showed high grade glioblastoma | CD4 468 at baseline; VL rebound weeks 25-32 (< 300 c/ml). Re-suppressed with addition of TDF/FTC thereafter. |
| 7. (PI-mono) | Anal carcinoma (week 80) | 56y male; smoker; anal mass detected; biopsy showed squamous cell carcinoma | CD4 319 at baseline; VL rebound weeks 24-43 (max 815 c/ml). Re-suppressed with addition of TDF/FTC thereafter. |

**Supplementary Table 3: Serious Adverse Events by category of event***

| | OT | PI-mono |
|---|---|---|
| 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 |

*Shown are the number of events in each category

**Supplementary Table 4: Grade 3 or 4 adverse events by Clinical and laboratory category ***

| | OT | PI-mono | Difference (95% CI) † | P |
|---|---|---|---|---|
| **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%) | 1.0 |
| Renal‡ | 2 (1%) [2] | 3 (1%) [3] | 0.3% (-1.4% to 2.1%) | 1.0 |
| CNS§ | 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%) | 0.0023 |
| Phosphate decreased | 73 (25%) | 37 (13%) | -12.6% (-18.8% to -6.3%) | <0.0001 |
| Bilirubin increased | 44 (15%) | 21 (7%) | -8.0% (-13.1% to -3.0%) | 0.0019 |
| 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 |

*Shown are the numbers of patients and the percentage of patients with a given type of Grade 3 or 4 adverse events, and the total number of events in each category. Recurrent laboratory events in the same patient were counted as a single event. P values were calculated for chi-square or Fisher's exact tests for the proportion of patients affected.

† Shown are absolute differences in the proportions of patients affected in each group

‡ Renal events were nephrolithiasis, pyelonephritis in 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 PI-mono group.

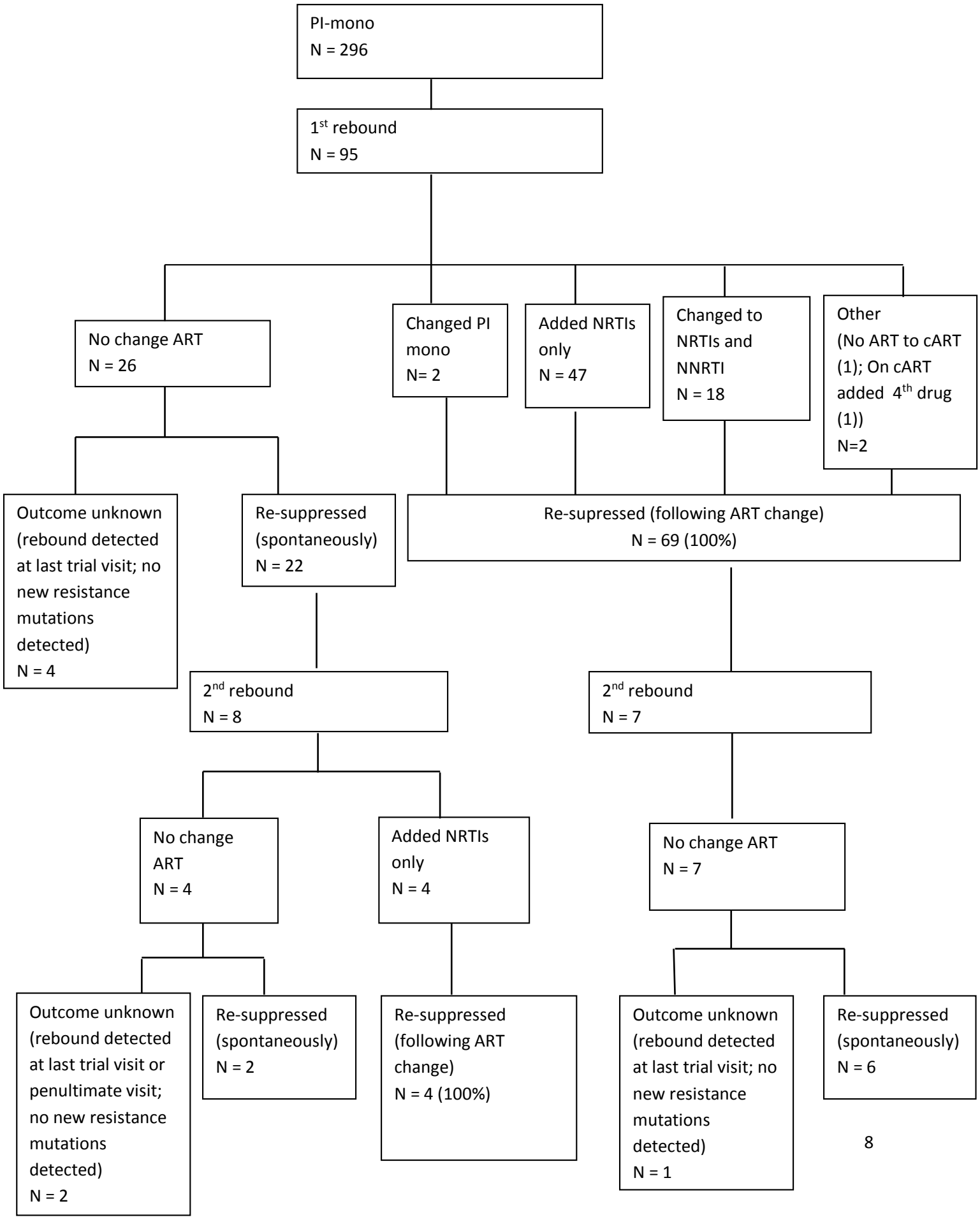
§ CNS events were depression and/or suicidal ideation (4), anxiety/stress (2), headache (2), psychosis (1), and normal pressure hydrocephalus (1) in the OT group; depression and/or suicidal ideation (9), anxiety/stress (1), headache (2), myasthenia gravis (1), psychosis (2); psychiatric symptoms, unspecified (1), meningioma (1), glioblastoma (1), head injury (1) and convulsion (1) in the PI-mono group

**Supplementary Table 5: Adverse events that were considered as related to antiretroviral therapy ***

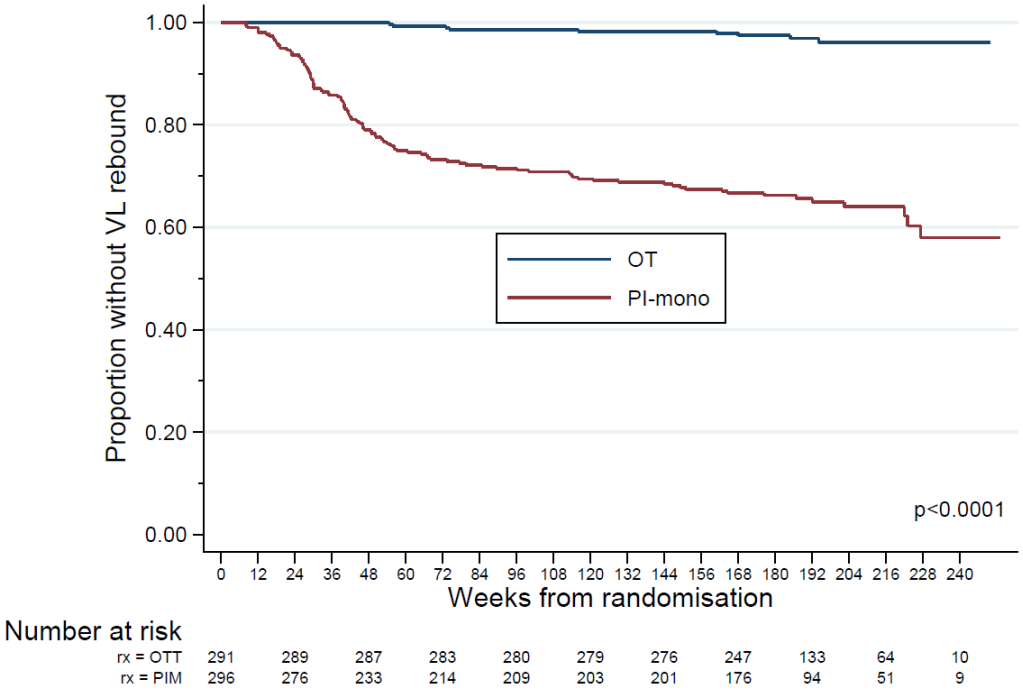
| | OT | PI-mono | Difference (95% CI) | P |
|---|---|---|---|---|
| Total | 6 (2.1%) [6] | 3 (1.0%) [3] | -1.0% (-3.2% to 1.1%) | 0.34 |
| Death | 0 | 0 | | |
| SAE | 2 | 0 | | |
| Grade 3/4 | 3 | 3 | | |
| SAE + Grade 3/4 | 1 | 0 | | |

* Shown are the total numbers of patients and the percentage of total patients with any event considered as possibly, probably or definitely related to antiretroviral therapy based on independent review at the coordinating centre. The number of events per category are shown for the individual categories. P value was calculated using Fisher's exact test for the proportion of patients affected.

**SUPPLEMENTARY FIGURE 1: Outcome of confirmed viral load rebound episodes in PI-mono arm**



**SUPPLEMENTARY FIGURE 2: Time to virological rebound - extended definition**




Extended definition of VL rebound included protocol-defined confirmed VL rebound cases as well as those that were changed earlier (i.e. at less than 4 weeks after the first detectable VL or after only 2 detectable VLs). Number (proportion) of rebound by end of follow-up: 9 (4.0%) in OT, and 105 (42.0%) in PI-mono (risk difference 38.0% [95%-CI: 29.2-46.8%]; P < 0.001). In PI-mono, rate of rebound is 27 per 100 person years in the first year, and 6 per 100 person years in subsequent years.