THE LANCET Infectious Diseases

Supplementary webappendix

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

Supplement to: Hakim JG, Thompson J, Kityo C, et al, for the Europe Africa Research Network for Evaluation of Second-line Therapy (EARNEST) Trial Team. Lopinavir plus nucleoside reverse-transcriptase inhibitors, lopinavir plus raltegravir, or lopinavir monotherapy for second-line treatment of HIV (EARNEST): 144-week follow-up results from a randomised controlled trial. *Lancet Infect Dis* 2017; published online Nov 3. http://dx.doi.org/10.1016/S1473-3099(17)30630-8.

SUPPLEMENTARY MATERIALS

Members of the EARNEST Trial Team are:

Participating Sites

Uganda

JCRC Kampala (African trial co-ordinating centre; 231) E Agweng, P Awio, G Bakeinyaga, C Isabirye, U Kabuga, S Kasuswa, M Katuramu, C Kityo, F Kiweewa, H Kyomugisha, E Lutalo, P Mugyenyi, D Mulima, H Musana, G Musitwa, V Musiime, M Ndigendawan, H Namata, J Nkalubo, P Ocitti Labejja, P Okello, P Olal, G Pimundu, P Segonga, F Ssali, Z Tamale, D Tumukunde, W Namala, R Byaruhanga, J Kayiwa, J Tukamushaba, S Abunyang, D Eram, O Denis, R Lwalanda, L Mugarura, J Namusanje, I Nankya, E Ndashimye, E Nabulime, D Mulima, O Senfuma.

IDI, Kampala (216): G Bihabwa, E Buluma, P Easterbrook, A Elbireer, A Kambugu, D Kamya, M Katwere, R Kiggundu, C Komujuni, E Laker, E Lubwama, I Mambule, J Matovu, A Nakajubi, J Nakku, R Nalumenya, L Namuyimbwa, F Semitala, B Wandera, J Wanyama

JCRC, Mbarara (97): H Mugerwa, A Lugemwa, E Ninsiima, T Ssenkindu, S Mwebe, L Atwine, H William, C Katemba, S Abunyang, M Acaku, P Ssebutinde, H Kitizo, J Kukundakwe, M Naluguza, K Ssegawa, Namayanja, F Nsibuka, P Tuhirirwe, M Fortunate

JCRC Fort Portal (66): J Acen, J Achidri, A Amone, M. Chamai, J Ditai, M Kemigisa, M Kiconco, C Matama, D Mbanza, F Nambaziira, M Owor Odoi, A Rweyora, G. Tumwebaze

San Raphael of St Francis Hospital, Nsambya (48): H Kalanzi, J Katabaazi, A Kiyingi, M Mbidde, M. Mugenyi, R Mwebaze, P Okong, I Senoga

JCRC Mbale (47): M Abwola, D Baliruno, J Bwomezi, A Kasede, M Mudoola, R Namisi, F Ssennono, S Tuhirwe

JCRC Gulu (43): G Abongomera, G Amone, J Abach, I Aciro, B Arach, P Kidega, J Omongin, E Ocung, W Odong, A Philliam

JCRC Kabale (33): H Alima, B Ahimbisibwe, E Atuhaire, F Atukunda, G Bekusike, A Bulegyeya, D. Kahatano, S Kamukama, J Kyoshabire, A Nassali, A Mbonye, T M Naturinda, Ndukukire, A Nshabohurira, H. Ntawiha, A Rogers, M Tibyasa;

JCRC Kakira (31): S. Kiirya, D. Atwongyeire, A. Nankya, C. Draleku, D. Nakiboneka, D. Odoch, L. Lakidi, R. Ruganda, R. Abiriga, M. Mulindwa, F. Balmoi, S. Kafuma, E. Moriku

Zimbabwe

University of Zimbabwe Clinical Research Centre, Harare (265): J Hakim, A Reid, E Chidziva, G Musoro, C Warambwa, G Tinago, S Mutsai, M Phiri, S Mudzingwa, T Bafana, V Masore, C Moyo, R Nhema, S Chitongo

Malawi

Department of Medicine, University of Malawi College of Medicine and the Malawi-Liverpool-Wellcome Trust Clinical Research Programme, University of Malawi College of Medicine (92): Robert Heyderman, Lucky Kabanga, Symon Kaunda, Aubrey Kudzala, Linly Lifa, Jane Mallewa, Mike Moore, Chrissie Mtali, George Musowa, Grace Mwimaniwa, Rosemary Sikwese, Joep van Oosterhout, Milton Ziwoya

Mzuzu Central Hospital, Mzuzu (19): H Chimbaka. B Chitete, S Kamanga, T Kayinga E Makwakwa, R Mbiya, M Mlenga, T Mphande, C Mtika, G Mushani, O Ndhlovu, M Ngonga, I Nkhana, R Nyirenda

Kenya

Moi Teaching and Referral Hospital (52): P Cheruiyot, C Kwobah, W Lokitala Ekiru, M Mokaya, A Mudogo, A Nzioka, A Siika, M Tanui, S Wachira, K Wools-Kaloustian

Zambia

University Teaching Hospital (37): P Alipalli, E Chikatula, J Kipaila, I Kunda, S Lakhi, J Malama, W Mufwambi, L Mulenga, P Mwaba, E Mwamba, A Mweemba, M Namfukwe

The Aids Support Organisation (TASO), Uganda: E Kerukadho, B Ngwatu, J Birungi

MRC Clinical Trials Unit: N Paton, J Boles, A Burke, L Castle, S Ghuman, L Kendall, A Hoppe, S Tebbs, M Thomason, J Thompson, AS Walker, J Whittle, H Wilkes, N Young, M Spyer

Monitors: C Kapuya, F Kyomuhendo, D Kyakundi, N Mkandawire, S Mulambo, S Senyonjo

Clinical Expert Review Committee: B Angus, A Arenas-Pinto, A Palfreeman, F Post, D Ishola

European Collaborators:

J Arribas (Hospital La Paz, Madrid, Spain), R Colebunders (Institute of Tropical Medicine, Antwerp, Belgium), M Floridia (ISS, Italy), M Giuliano (ISS, Italy), P Mallon (University College Dublin, Ireland), P Walsh (University College Dublin, Ireland), M De Rosa (CINECA, Italy), E Rinaldi (CINECA, Italy)

Trial Steering Committee: I Weller (Chair), C Gilks, J Hakim, A Kangewende, S Lakhi, E Luyirika, F Miiro, P Mwamba, P Mugyenyi, S Ojoo, N Paton, S Phiri, J van Oosterhout, A Siika, S Walker, A Wapakabulo,

Data Monitoring Committee: T Peto (Chair), N French, J Matenga

Pharmaceutical companies: G Cloherty, J van Wyk, M Norton, S Lehrman, P Lamba, K Malik, J Rooney, W Snowden, J Villacian

SUPPLEMENTARY METHODS

Factors/subgroups tested were VL and CD4 count at switch, duration of first-line ART, NRTIs taken during first-line and at failure, and NRTIs specified by physicians prior to randomisation that they would prescribe if the patients were randomised to PI/NRTI (available for both groups, in contrast to actual NRTIs prescribed which is only available for PI/NRTI), viral subtype (based on available genotypes), presence of intermediate-high resistance to NRTIs, number of NRTIs available with susceptibility/low-level resistance, presence of M184V mutation, a future options genotypic susceptibility score (GSS; obtained from the total of the scores for predicted susceptibility of 3TC/FTC, ABC, D4T, DDI, TDF and ZDV determined using the Stanford algorithm according to predicted susceptibility), adherence to second-line (percentage of visits reporting missing pills in the last month, missed, or attended over 7 days late) and self-reported alcohol consumption during second-line, and employment status. VL, CD4, and duration of first-line ART were subgroups specified in the Statistical Analysis plan; other factors were exploratory.

SUPPLEMENTARY TABLES

Supplementary Table 1: Early virological responses on second-line therapy by randomized group

	PI/NRTI	PI/RAL	Difference PI/RAL-PI/NRTI (95% CI)	P value
Week 4				
Available, N	374	389		
VL<50 copies/ml, N (%)	31 (8%)	125 (32%)	+23.8% (+18.4%, +29.3%)	<0.0001
VL<400 copies/ml, N (%)	180 (48%)	333 (86%)	+37.5% (+31.3%, +43.6%)	<0.0001
VL<1000 copies/ml, N (%)	278 (74%)	360 (93%)	+18.2% (+13.1%, +23.4%)	<0.0001
Change in log_{10} VL from baseline, mean (95% CI)*	-2.13 (-2.22, -2.03)	-2.88 (-2.97, -2.78)	-0.75 (-0.88, -0.62)	<0.0001
Week 12				
Available, N	381	394		
VL<50 copies/ml, N (%)	163 (43%)	259 (66%)	+23.0% (+16.1%, +29.8%)	<0.0001
VL<400 copies/ml, N (%)	335 (88%)	361 (92%)	+3.7% (-0.6%, +8.0%)	0.09
VL<1000 copies/ml, N (%)	357 (94%)	367 (93%)	-0.6% (-4.0%, +2.9%)	0.76
Week 24				
Available, N	382	389		
VL<50 copies/ml, N (%)	266 (70%)	299 (77%)	+7.2% (+1.0%, +13.5%)	0.02
VL<400 copies/ml, N (%)	341 (89%)	358 (92%)	+2.8% (-1.3%, +6.9%)	0.19
VL<1000 copies/ml, N (%)	350 (92%)	363 (93%)	+1.7% (-2.0%, +5.4%)	0.37

*Declines in log_{10}VL from baseline to week 4 and 12 were compared between the PI/NRTI and PI/RAL groups (PI-mono same as PI/RAL to week 12) using interval regression (left censoring those <40 copies/ml at week 4 at 0 log_{10} copies/ml; similar results censoring at 39 log_{10} 39 copies/ml, not shown).

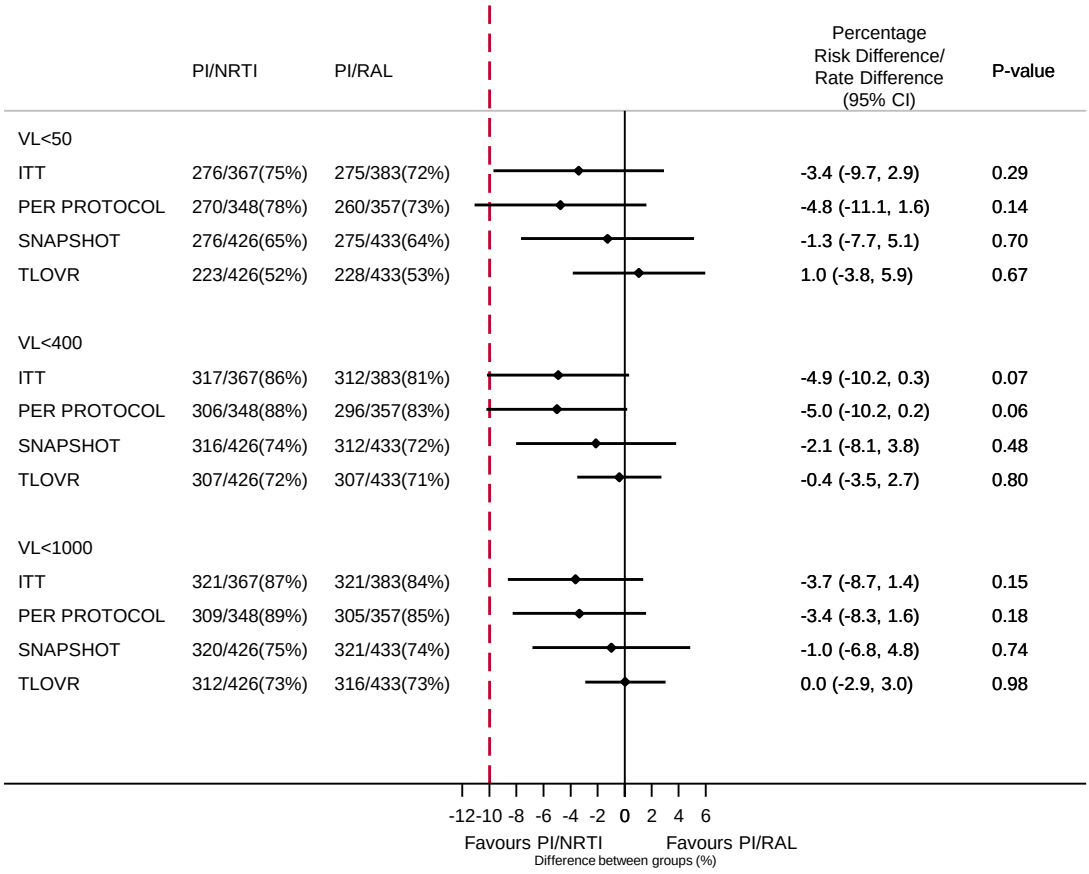
Supplementary Table 2: Serious Adverse Events to week 144, by category

	PI/NRTI (N=426)	PI/RAL (N=433)	PI-mono (N=418)
SAE – n patients (%)	113 (27%)	106 (24%)	99 (24%)
Total SAEs	139	127	131
Fatal	42	33	31
Life threatening	18	18	13
Caused or prolonged hospitalisation	98	89	92
Persistent or significant disability/incapacity	1	3	1
Congenital anomaly/ birth defect	0	0	0
Other important medical condition	3	7	11

Table shows number of patients experiencing an SAE (n, %) followed by the total number of SAEs (a patient may have more than one SAE)

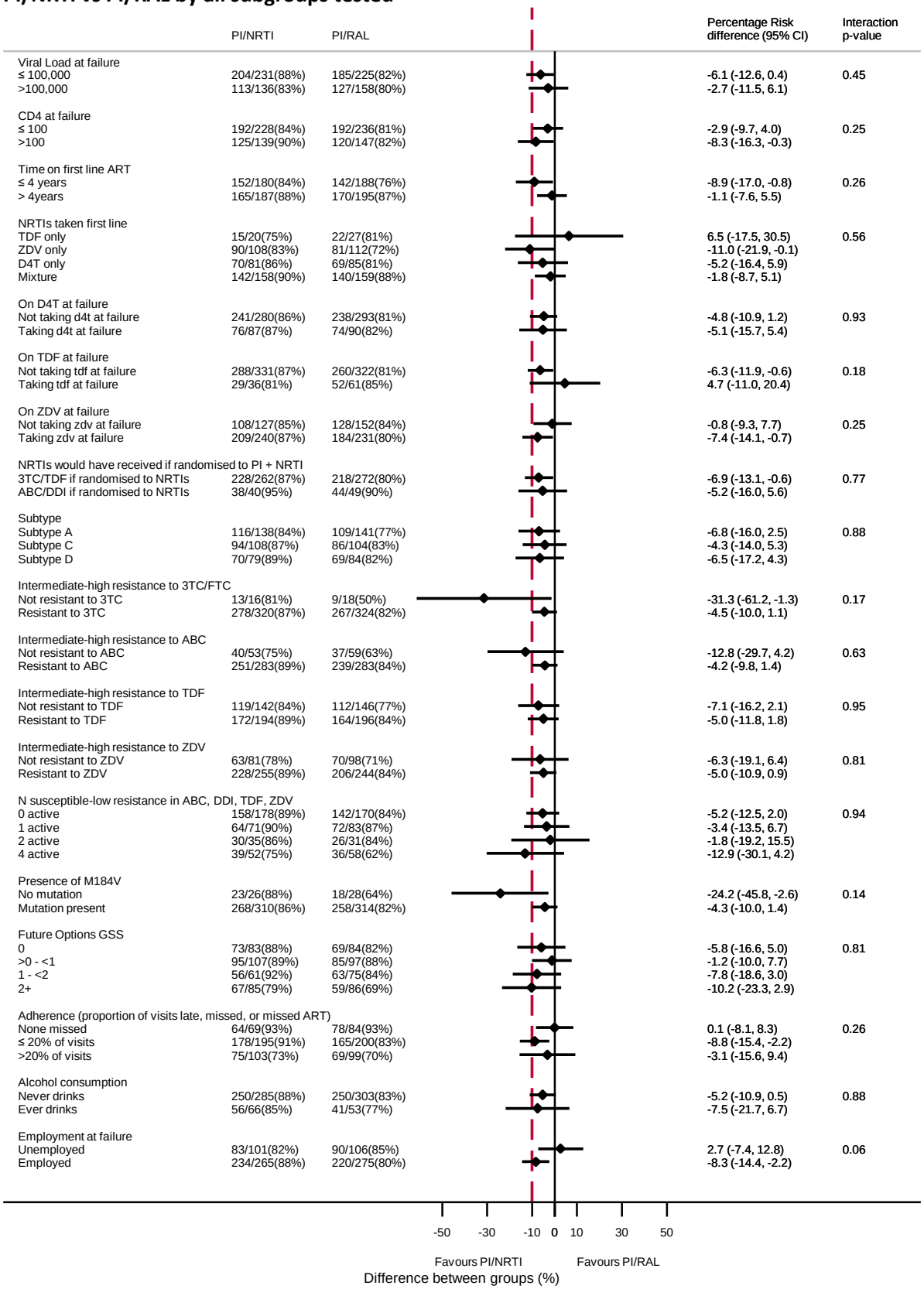
SUPPLEMENTARY FIGURES

Supplementary Figure 1: Plasma VL<400 copies/ml 144 weeks after switch to second-line in PI/NRTI vs PI/RAL by analysis approach



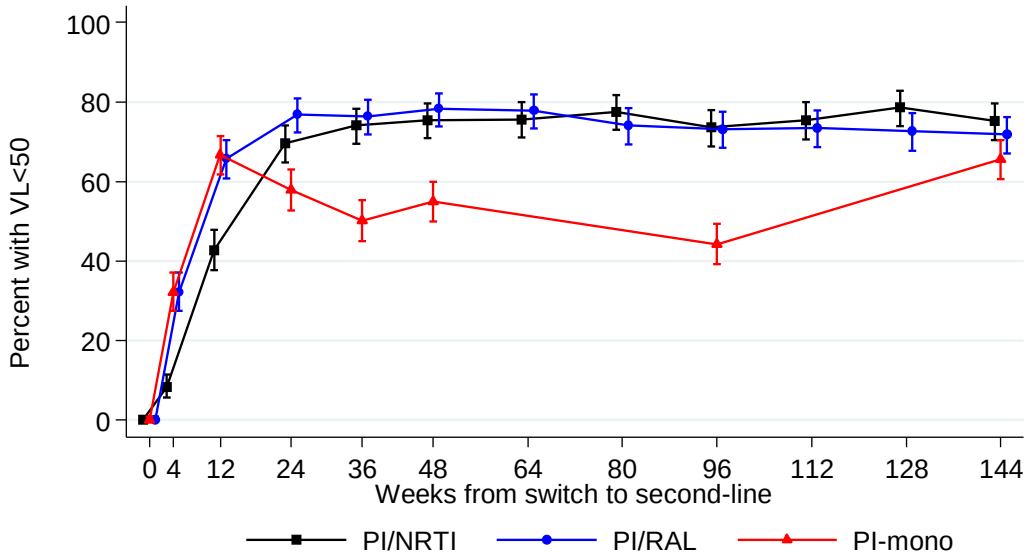
TLOVR result given as absolute rate difference per 100 person years

Supplementary figure 2: Plasma VL<400 copies/ml 144 weeks after switch to second-line in PI/NRTI vs PI/RAL by all subgroups tested



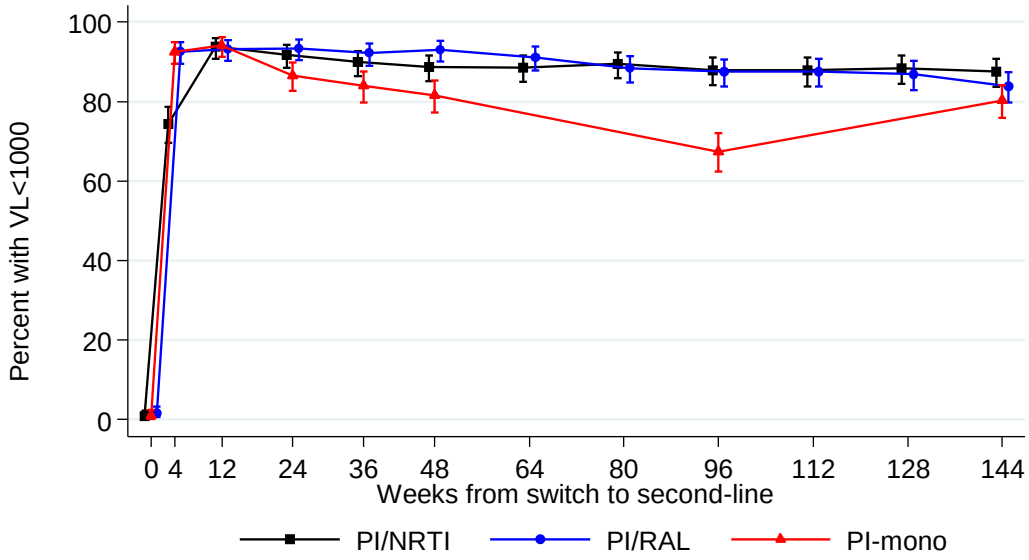
Note: See Supplementary Methods for details on factors tested.

Supplementary Fig 3a: Plasma VL<50 copies/ml to week 144 in the three second-line treatment groups



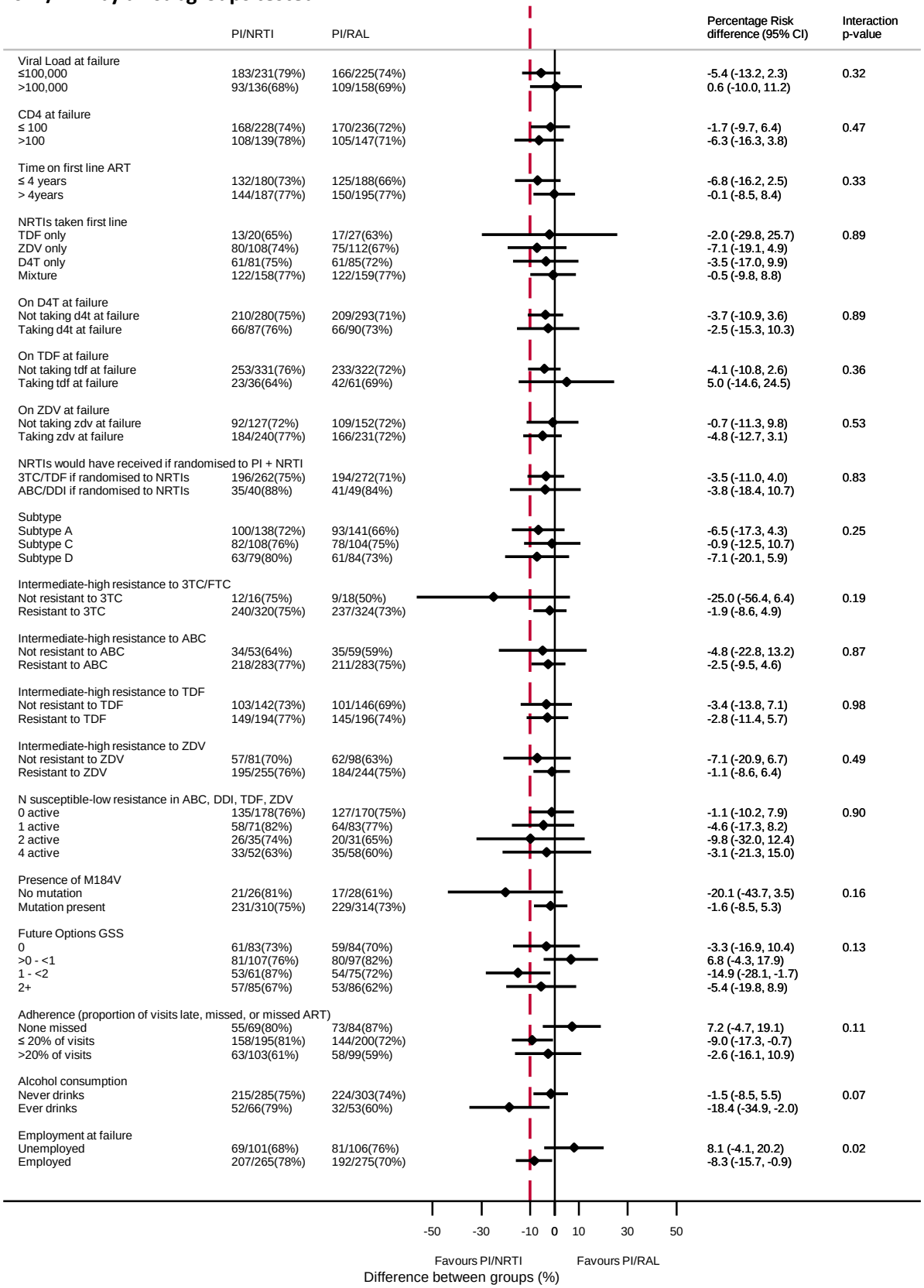
P values comparing the groups by Generalised Estimating Equations across all weeks from week 36 onwards (testing any direction of effect):
Global GEE p<0.0001
PI/RAL vs PI/NRTI GEE p=0.19
PI-mono vs PI/NRTI GEE p<0.0001

Supplementary figure 3b: Plasma VL<1000 copies/ml to week 144 in the three second-line treatment groups



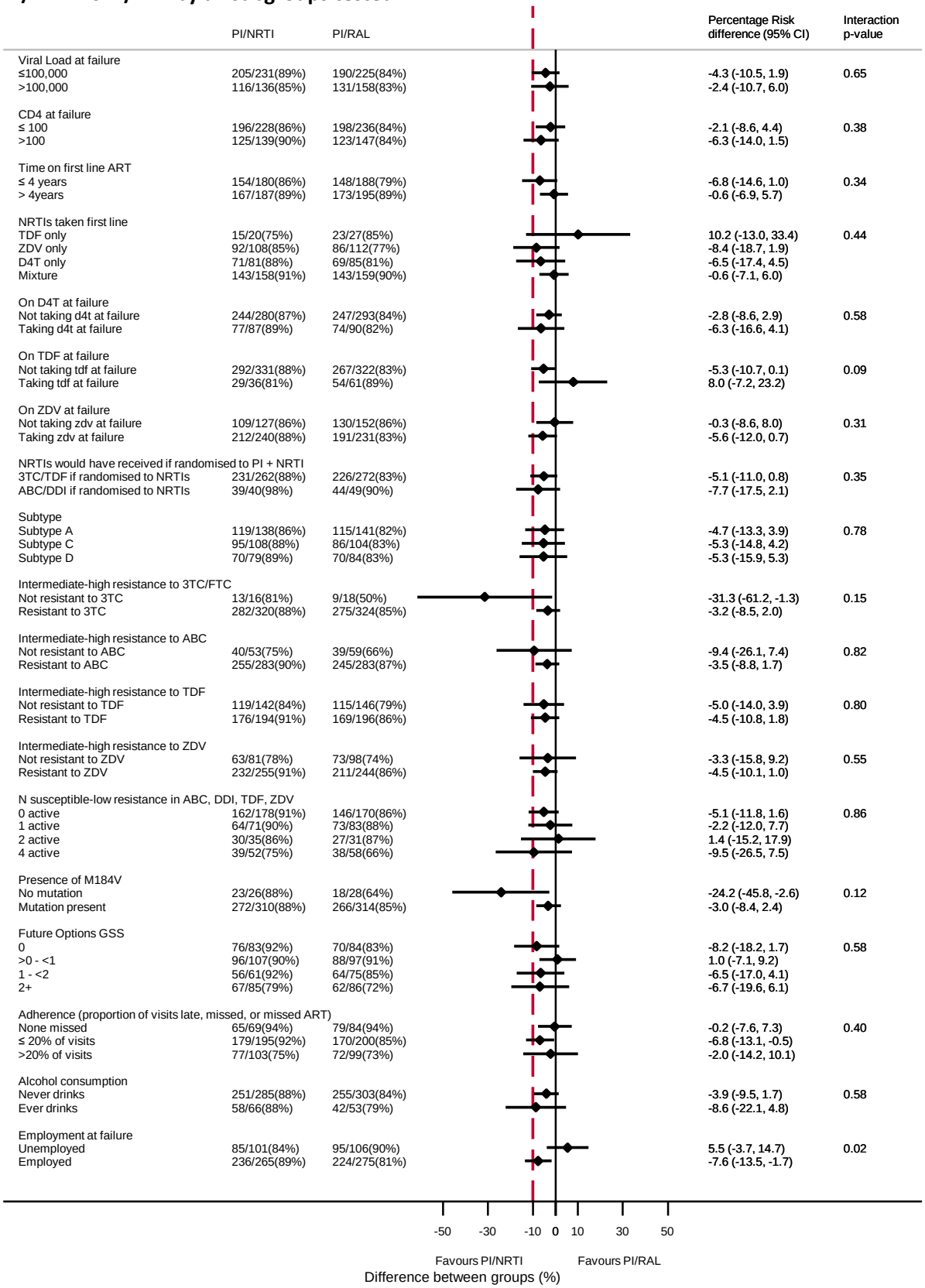
P values comparing the groups by Generalised Estimating Equations across all weeks from week 36 onwards (testing any direction of effect):
Global GEE p<0.0001
PI/RAL vs PI/NRTI GEE p=0.07
PI-mono vs PI/NRTI GEE p<0.0001

Supplementary figure 4: Plasma VL<50 copies/ml 144 weeks after switch to second-line in PI/NRTI vs PI/RAL by all subgroups tested



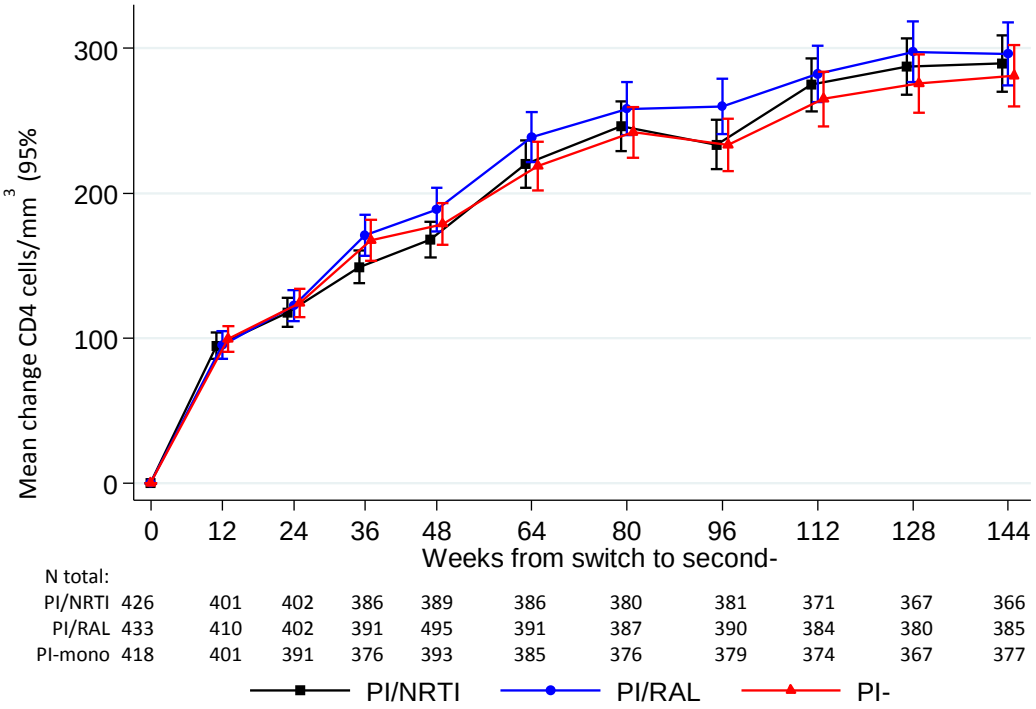
Note: See Supplementary Methods for information on factors tested. 19 subgroup analyses performed, and therefore ~1 interaction p-value would be expected to be <0.05 by chance

Supplementary figure 5: Plasma VL<1000 copies/ml at 144 weeks after switch to second-line in PI/NRTI vs PI/RAL by all subgroups tested



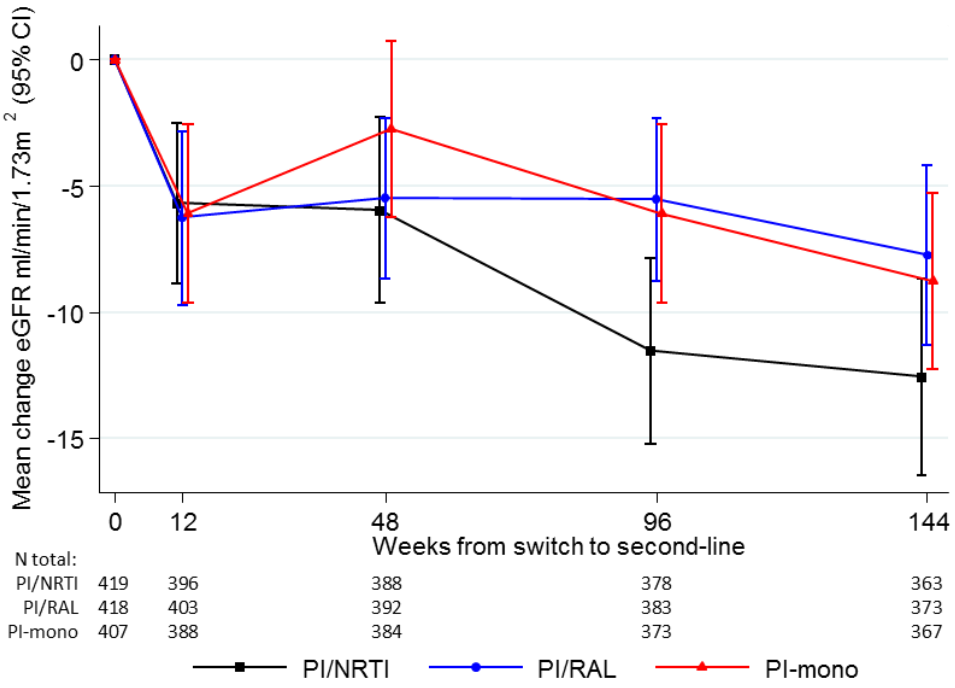
Note: See footnote to Figure 2 for information on factors tested. 19 subgroup analyses performed, and therefore ~1 interaction p-value would be expected to be <0.05 by chance

Supplementary figure 6: Change in CD4 count to week 144 by treatment group



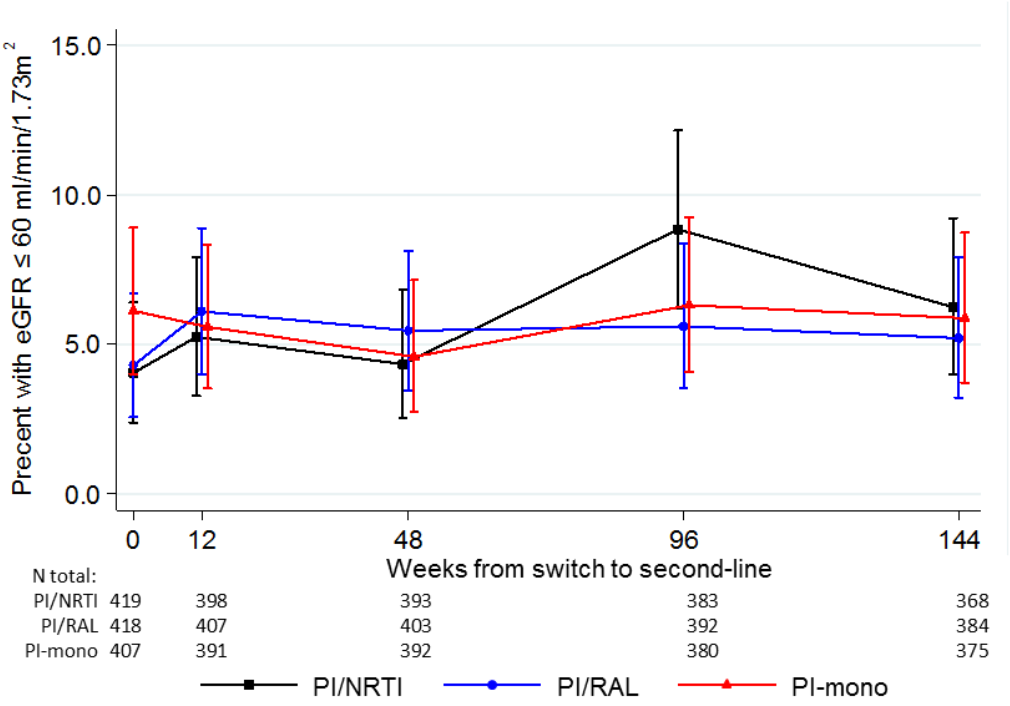
P values comparing the groups by Generalised Estimating Equations across all weeks (testing any direction of effect):
Global GEE p=0.11
PI/RAL vs PI/NRTI GEE p=0.04
PI-mono vs PI/NRTI GEE p=0.30

Supplementary figure 7a: Change in eGFR to week 144 by treatment group



P values comparing the groups by Generalised Estimating Equations across all weeks (testing any direction of effect):
Global GEE p=0.06
PI/RAL vs PI/NRTI GEE p=0.02
PI-mono vs PI/NRTI GEE p=0.21

Supplementary figure 7b: Proportion with grade 2 or higher eGFR to week 144 by treatment group



P values comparing the groups by Generalised Estimating Equations across all weeks (testing any direction of effect):
Global GEE p=0.52
PI/RAL vs PI/NRTI GEE p=0.16
PI-mono vs PI/NRTI GEE p=0.62