Appendix 3: GRADE Tables

3.3. Switch studies: simplification – PI monotherapy

Design: RCTs, Systematic reviews
Population: ART experienced, stable on ART, undetectable VL
Intervention: regimen simplification- PI monotherapy (darunavir or lopinavir)
Outcomes: Viral load, CD4 count, HIV resistance, adverse events, clinical events

NB Outcomes data extracted from main report of study at primary time point (e.g. 48 weeks). Data not extracted again for other time points in the same paper, or other papers from the same study, where this would double count the same patients (e.g. at week 96); data from secondary reports of the same study only added to analysis if different outcomes reported (not in main paper).

Systematic reviews
Mathis, S., B. Khanlari, et al. (2011). "Effectiveness of Protease Inhibitor Monotherapy versus Combination Antiretroviral Maintenance Therapy: A Meta-Analysis." PLoS ONE [Electronic Resource] **6(7):

This meta-analysis includes data from 10 trials (cut off date for search August 2010): 9 included among those reported below (covering the OK pilot study, OK04, KalMo, Cohn study, KALESOLO, MONOI and MONET trials) plus Echeverria P, Domingo P, Gutierrez M, Mateo G, Fuster M, et al. (2010) Saqinavir/ritonavir monotherapy as a new nucleoside sparing maintenance strategy in long-term virologically suppressed HIV-infected patients. Curr HIV Res 8: 467–70. This was excluded from our review as it assesses saquinavir, which is not used as monotherapy.

Our analysis below includes 18 studies (9 overlapping with Mathis review, plus 5 more papers covering aspects of the MONET trial; 3 more OK04; and one paper describing the KAMON2 trial published as an abstract in 2011).

MONET trial

1. ** Arribas, J. R., A. Horban, et al. (2010). "The MONET trial: darunavir/ ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/ml." AIDS **24**(2): 223-230.

Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Arribas, J. R., A. Horban, et al. (2010). "The MONET trial: darunavir/ ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/ml." AIDS **24**(2): 223-230.	**RCT** **Allocation to treatment** Random Method of randomisation: unclear Concealment: unclear **Blinding** not blinded **Sample size calculation** stated **ITT analysis** Yes **Setting:** Outpatients	**Total N: 256** 10 pts were excluded from the per protocol population (4 monotherapy, 6 triple therapy). 8 of these pts had a history of virological failure before the trial, 1 was imprisoned and 1 left the investigational site indefinitely. Data from 246 pts (123 per arm) were included in the per protocol population. All 256 pts in the	**INCLUSION CRITERIA** HIV RNA levels below 50 copies/ml on stable triple antiretroviral regimen for at least 24 weeks and no history of virological failure since first starting antiretrovirals. **EXCLUSION CRITERIA** not stated **Baseline comparability between groups**: Pts on triple therapy were more likely to be on their 1st antiretroviral regimen (36%) than pts on monotherapy (23%); pts on triple therapy were more likely to be protease inhibitor-naive (28%) than on monotherapy (23%). By hepatitis C serology, 22 (17%) patients had hepatitis C antibodies on monotherapy and 12 (9%)	**n=127** **Drug(s):** darunavir / ritonavir 800/100 mg once daily	**n=129** **Drug(s):** triple therapy arm of two nucleoside analogues (selected by the investigators) and darunavir / ritonavir 800/100 mg once daily. Nucleoside analogues used at baseline	**Treatment duration:** 48 weeks **Assessments at:** screening, baseline and then weeks 4, 12, 24, 36 and week 48 **Follow-up after end of treatment:** none	**Primary endpoint:** treatment failure, defined as two consecutive HIV RNA levels above 50 copies/ml at week 48, or discontinuation of randomized treatment [commonly known as time to loss of virological response (TLOVR)] Other endpoints: Safety assessments included	Janssen-Cilag

		ITT population were included in the safety analysis.	on triple therapy. At baseline, 13 patients had HIV RNA levels above 50 copies/ml (nine on monotherapy and 4 on triple therapy), despite having results below 50 copies/ml at screening; 2 of these elevations were above 400 copies/ml. These pts were still included in both the per protocol and ITT analyses. **Age**: mean 44 years **Gender**: 81% male **Severity of disease:** mean CD4 cell count 574 cells/ml **Duration of disease**: median 8 years of known HIV infection, and median of 6.5 years treatment with antiretrovirals		were: tenofovir + emtricitabine (46%), tenofovir + lamivudine (7%), abacavir + lamivudine (31%), zidovudine + lamivudine (10%), or other (6%).		reported adverse events data, clinical laboratory tests (haematology, clinical chemistry, fasting lipids, and urinalysis), physical examination and anthropometric measurements. Clinical and laboratory abnormalities	

Main outcomes:

Summary HIV RNA less than 50 copies/ml at week 48, for the per protocol (PP) and intent to treat (ITT) populations.

Response	Monotherapy (%)	Triple therapy (%)	Delta (95% CI)
HIV RNA<50 (PP)	86.2 (n=106/123)	87.8 (n=108/123)	-1.6% (-10.1, +6.8%) i.e. non-inferior
HIV RNA<50 (ITT)	84.3 (n=107/127)	85.3 (n=110/129)	-1.0% (-9.9, +8.8%) i.e. non-inferior

Other outcomes:

Median CD4 cell counts remained stable over time in both treatment arms (no data shown).

	Monotherapy arm (n=127):	Triple therapy (n=129):
Protocol defined treatment failures: confirmed HIV RNA elevations missing HIV RNA data discontinued for adverse events discontinued for other reasons	20 11 0 4 5	19 7 3 0 9
Of the protocol defined treatment failures: HIV RNA levels below 50 copies/ml at week 48	18/20 (90%)	17/19 (89%)
Of those with confirmed HIV RNA elevations, number who changed their antiretrovirals as recommended in the trial protocol	7/ 11 (either adding NRTIs, or switching back to pretrial antiretrovirals)	0/7

Genotypic data were available for 35 of 61 (57%) patients with at least one HIV RNA result above 50 copies/ml (22 and 13 patients in the monotherapy and triple therapy arms, respectively). Thirty-three of these patients showed genotypic and phenotypic sensitivity to all boosted protease inhibitors and NRTIs. One protease inhibitor-pretreated patient in the triple therapy arm had a single genotype, showing resistance to lamivudine (M184V) and to protease inhibitors (V82IT, L90M), when the HIV RNA level was 78 copies/ml. However, the virus was phenotypically sensitive to DRV/r (fold change=1.2). All subsequent visits showed HIV RNA levels below 50 copies/ml. Also, one protease inhibitor-pretreated patient in the monotherapy arm had a single DRV mutation (L33F), when the HIV RNA level was 63 copies/ml at one visit (week 12). However, the virus was phenotypically sensitive to DRV (fold change=0.8) and HIV RNA was suppressed below 50 copies/ml for this patient for all subsequent visits to week 48.

	Monotherapy arm (n=127):	Triple therapy (n=129):
Serious adverse events	9 pts	9 pts
Discontinued study medication for adverse events	8 pts	3 pts
Deaths	0	0
Grade 1–4 adverse events of the nervous system	16% (20 pts)	16% (21 pts)
Grade 1–4 psychiatric adverse events	9%	9%
Discontinued darunavir for grade 3 headache, considered to be drug related	1 pt	0
Grade 2 rash, considered drug-related	1 pt	1 pt
Discontinued the trial for rash	0	0
Grade 3 elevations in alanine aminotransferase and/or aspartate aminotransferase (these patients all had either acute infection with HCV (two cases), presence of HCV antibodies (five cases) or acute hepatitis A infection (one case). Six of these eight patients showed transient elevations in liver enzymes, with values at grade 1 or below at week 48)	6 pts	2 pts

Treatment emergent grade 3 elevations in total cholesterol, sustained for at least two consecutive visits	5 pts	2 pts
At least one red blood cell result below the lower limit of normal (<4.12 x 10^{12}/l)	22.8%	42.6%

Authors' conclusion

Once-daily DRV/r monotherapy has been shown to be noninferior HIV RNA suppression at week 48 (85.4%) compared with a standard control arm of two nucleosides and DRV/r (86.4%). Almost all patients on DRV/r monotherapy had full HIV RNA suppression, at week 48 in the MONET trial: although this strategy warrants further evaluation, these data suggest that a switch to DRV/r monotherapy can be considered in treatment-experienced patients who have a history of HIV RNA levels below 50 copies/ml on other treatments, but who are wishing to avoid toxicities related to nucleoside analogues, non-nucleosides or other antiretrovirals.

2. ** Clumeck, N., A. Rieger, et al. (2011). "96 week results from the MONET trial: a randomized comparison of darunavir/ritonavir with versus without nucleoside analogues, for patients with HIV RNA <50 copies/mL at baseline." Journal of Antimicrobial Chemotherapy **66**(8): 1878-1885.

Reference: Clumeck, N., A. Rieger, et al. (2011). "96 week results from the MONET trial: a randomized comparison of darunavir/ritonavir with versus without nucleoside analogues, for patients with HIV RNA <50 copies/mL at baseline." Journal of Antimicrobial Chemotherapy **66**(8): 1878-1885.

MONET trial: methodology as above except this paper reports 96 week outcomes

Main outcomes:

Efficacy endpoint, week 96	Monotherapy n=127	Triple therapy n=129	Difference (95% CI)
HIV RNA <50 copies/mL, switch=failure, TLOVR, per protocol	95/122 (78%)	101/123 (82%)	-4.2% (-14.3%, +5.8%)
HIV RNA <50 copies/mL, switch=failure, TLOVR, ITT	95/127 (75%)	104/129 (81%)	-5.8% (-16.0%, +4.4%)

Median CD4 counts remained stable over time in both treatment arms (no data shown).

	Monotherapy arm (n=127):	Triple therapy (n=129):
Protocol defined treatment failures: confirmed HIV RNA elevations withdrew from the trial before week 96 (started new antiretrovirals)	32 15 17 without prior virological failure	25 11 14 (12 without virological failure; 1 known virological

		failure; 1 missing data)
Of the confirmed HIV RNA elevations: HIV RNA levels below 50 copies/ml at week 96/most recent visit	11/15	10/11
Of those with confirmed HIV RNA elevations, number who changed their antiretrovirals as recommended in the trial protocol	9/15 (either adding nucleoside reverse transcriptase inhibitors (NRTIs) or switching back to pre-trial antiretrovirals)	0/11

76 pts (41 on monotherapy, 35 on triple therapy) had at least one HIV RNA result >50 copies/mL during the trial and were genotyped. Genotyping was successful for 48 patients (21 and 27 patients in the monotherapy and triple therapy arms, respectively). 46 of these 48 pts (96%) showed genotypic and phenotypic sensitivity to all boosted PIs and NRTIs. Major IAS–USA PI mutations were detected in one pt per treatment arm, during short-term elevations in HIV RNA. In the monotherapy arm, the L33F mutation was detected at a single visit, when the HIV RNA level was 63 copies/mL. In the triple therapy arm, PI mutations detected before the trial re-emerged, when the HIV RNA level was 78 and 50 copies/mL during an interruption of treatment. Both pts remained phenotypically sensitive to darunavir during follow-up, with sustained HIV RNA ,50 copies/ mL during the trial and no change in antiretroviral treatment.

	Monotherapy arm (n=127):	Triple therapy (n=129):
Serious adverse events	13 pts (10.2%)	13 pts (10.1%)
Deaths	0	0
Grade 1–4 adverse events of the nervous system Grade 2–4 adverse events of the nervous system	25 (19.4%) 10 (7.8%)	29 (22.8%) 10 (7.9%)
Grade 1–4 psychiatric adverse events Grade 2–4 psychiatric adverse events	20 (15.5%) 9 (7.0%)	15 (11.8%) 11 (8.7%)
Grade 3 nervous system or psychiatric adverse event	1 (pt discontinued treatment for headache)	2: 1 pt had grade 3 depression and 1 had a loss of libido.
Neuropsychiatric adverse events that would suggest CNS viraemia	0	0
Grade 3–4 abnormalities in alanine aminotransferase *	8 (6.3%)	3 (2.4%)
Grade 3–4 abnormalities in aspartate transaminase *	5 (3.9%)	3 (2.4%)
Grade 3–4 abnormalities in lipase	4 (3.2%)	3 (2.4%)
Grade 3–4 abnormalities in low-density lipoprotein	12 (9.4%)	10 (7.8%)
Grade 3–4 abnormalities in total cholesterol of whom elevations at a single timepoint only sustained elevations	14 (11.0%) 8/14 6/14	5 (3.9%) 2/5 3/5
Grade 3–4 abnormalities in triglycerides	4 (3.2%)	1 (0.8%)

Grade 3–4 abnormalities in haemoglobin	0	2 (1.6%)
Grade 3–4 abnormalities in neutrophils	0	2 (1.6%)
Grade 1–4 haematuria of which grade 3 (severe)	4 1 (this pt had stopped taking tenofovir at the baseline visit)	12 (of whom 8 receiving tenofovir) 6
Clinical adverse events at least one grade 1–4 adverse event	112 (86.8%)	109 (84.5%)

*Elevations in alanine transaminase and aspartate transaminase were associated with acute or chronic infection with hepatitis A or hepatitis C.

Authors' conclusion
These results suggest that the strategy of switching to darunavir/ritonavir monotherapy can be considered in treatment-experienced patients who have a history of HIV RNA levels <50 copies/mL on other treatments, but who wish to avoid toxicities related to nucleoside analogues, non-nucleosides or other antiretrovirals. If necessary, patients who show low-level elevations in HIV RNA during darunavir/ritonavir monotherapy can be successfully re-intensified with nucleoside analogues to re-suppress HIV RNA below detectable levels.

3. * Garvey, L., C. Higgs, et al. (2010). "Changes in cerebral function parameters in HIV-1 infected subjects undergoing a treatment simplification to darunavir/ritonavir :A randomized, prospective study." Antiviral Therapy **15**: A70. 12TH Int Workshop on Adverse drug reactions and co-morbidities P42 **(conference abstract)-** published AIDS Research and Human retroviruses 2011; 27 (7): 701-703 (**letter**)
   According to the protocol this study should be excluded as it is only published as a letter (very small sub-sample of MONET, n=6)

4. * Gazzard, B., A. Hill, et al. (2011). "Cost-efficacy analysis of the MONET trial using UK antiretroviral drug prices." Applied Health Economics & Health Policy **9**(4): 217-223.

Reference: Gazzard, B., A. Hill, et al. (2011). "Cost-efficacy analysis of the MONET trial using UK antiretroviral drug prices." Applied Health Economics & Health Policy **9**(4): 217-223.

MONET trial: methodology as above except the purpose of this analysis was to calculate the potential cost savings from the use of DRV/r monotherapy in the UK. The UK costs per patient with HIV RNA <50 copies/mL at week 48 (responders) were calculated using a 'switch included' analysis to account for additional antiretrovirals taken after initial treatment failure. By this analysis, efficacy was 93.5% versus 95.1% in the DRV/r monotherapy and triple therapy arms, respectively. *British National Formulary* 2009 values were used.

Main outcomes:
Before the trial, the mean annual cost of antiretrovirals was £6906 for patients receiving NNRTI-based HAART, and £8348 for patients receiving PI-based HAART. During the MONET trial, the mean annual per-patient cost of antiretrovirals was £8642 in the triple therapy arm, of which 55% was from NRTIs and 45% from PIs. The mean per-patient cost in the monotherapy arm was £4126, a saving of 52% versus triple therapy. The mean cost per responder was

£9085 in the triple therapy arm versus £4413 in the DRV/r monotherapy arm.

Authors' conclusion
Based on the MONET results, the lower cost of DRV/r monotherapy versus triple therapy in the UK would allow more patients to be treated for fixed budgets, while maintaining HIV RNA suppression at <50 copies/mL. If all patients meeting the inclusion criteria of the MONET trial in the UK were switched to DRV/r monotherapy, there is the potential to save up to £60 million in antiretroviral drug costs from the UK NHS budget.

5. * Pulido, F., J. R. Arribas, et al. (2011). "Analysis of drug resistance during HIV RNA viraemia in the MONET trial of darunavir/ritonavir monotherapy." Antiviral Therapy **16**(1): 59-65.

Reference: Pulido, F., J. R. Arribas, et al. (2011). "Analysis of drug resistance during HIV RNA viraemia in the MONET trial of darunavir/ritonavir monotherapy." Antiviral Therapy **16**(1): 59-65.

MONET trial: methodology as above except this paper only reports on drug resistance.

Main outcomes:
The results are a duplicate of those reported in the Arribas 2010 paper reported above and are not data extracted again to avoid double counting the same patients.

Authors' conclusion
Drug resistance to PIs in the MONET trial was uncommon.

6. *Winston, A., G. Fatkenheuer, et al. (2010). "Neuropsychiatric adverse events with ritonavir-boosted darunavir monotherapy in HIV-infected individuals: a randomised prospective study." HIV Clinical Trials **11**(3): 163-169

Reference: Winston, A., G. Fatkenheuer, et al. (2010). "Neuropsychiatric adverse events with ritonavir-boosted darunavir monotherapy in HIV-infected individuals: a randomised prospective study." HIV Clinical Trials **11**(3): 163-169

MONET trial: methodology as above except this paper reports clinician-reported neuropsychiatric events (clinical adverse events graded by severity as either grade 1 (mild), grade 2 (moderate), grade 3 (severe), or grade 4 (life-threatening) and whether adverse events were related to study medication using the Division of AIDS 2007 classification system) and patient-reported neuropsychiatric events (self-scored memory and concentration assessment using part of the Functional Assessment of HIV Infection (FAHI) questionnaire, and an assessment of cognitive function) over 48 weeks.

Main outcomes:

Grade 1–4 central nervous system and psychiatric adverse events by treatment arm

	DRVrMono (n=127)	DRVrNRTI (n=129)
All CNS adverse events, n (%)	20 (15.7%)	21 (16.3%)
Arefl exia	0	1
Burning sensation	0	1
Carotid artery stenosis	1	0
Disturbance in attention	0	1
Dizziness	1	3
Dysgeusia	1	1
Headache	10	9
Hypoasthaesia	2	1
Intracranial hypotension	1	0
Nervous system disorder	0	1
Parasthaesia	2	0
Post herpetic neuralgia	1	0
Cervical radiculitis	0	2
Sciatica	0	1
Syncope	2	0
Tremor	0	1
Trigeminal neuralgia	1	0
All psychiatric adverse events, n (%)	12 (9.4%)	12 (9.3%)
Anxiety disorder	0	1
Apathy	1	0
Depression	7	3
Drug dependence	0	2
Insomnia	0	3
Libido decreased	1	1
Nightmare	0	1
Obsessive-compulsive disorder	1	0
Psychotic disorder	1	0
Sleep disorder	4	5
Stress	0	1

Most of these events were grade 1 (mild) in severity and not judged to be related to study medication. The most frequently observed CNS adverse event was headache (reported by 19 patients), while the most frequently observed psychiatric adverse event was depression (reported by 10 patients). Of the 32 grade 1–4 neuropsychiatric adverse events in the DRVrMono arm, two were grade 2–4 and drug related (both cases were of headache); of the 33 grade 1–4 neuropsychiatric adverse events in the DRVrNRTI arm, three were judged grade 2–4 and drug related (headache, migraine, and cervical radiculitis). One patient in the DRVrMono arm discontinued darunavir for a grade 3 headache.

Change from baseline in FAHI cognitive functioning score:

	Week 24		Week 48		
Study group	Mean ± *SD*	No. of subjects	Mean ± *SD*	No. of subjects	*P* value for difference in change between study treatment groups at week 48, Student *t* test.
Overall	0.2 ± 2.8	211	0.1 ± 2.6	206	0.76
DRVrMono	0.1 ± 2.7	99	0.0 ± 2.7	95	
DRVrNRTI	0.4 ± 2.9	112	0.1 ± 2.5	111	

Authors' conclusion
In this exploratory analysis, no differences in the evolution of neuropsychiatric adverse events over 48 weeks are observed in HIV-infected subjects randomised to switch antiretroviral therapy to darunavir/ritonavir with or without nucleoside reverse transcriptase inhibitors.

7. * The MONET trial: week 144 analysis of efficacy of darunavir/ritonavir monotherapy versus DRV/r + 2NRTIs, for patients with HIV RNA < 50 copies/mL at baseline. J. Arribas, N. Clumeck, M. Nelson, A. Hill, Y. van Delft, C. Moecklinghoff. abstract no. MOPE216, IAS 2011 **(conference abstract)**
   Same patients and outcome measures as above – not data extracted again as would be double counting.

Reference: The MONET trial: week 144 analysis of efficacy of darunavir/ritonavir monotherapy versus DRV/r + 2NRTIs, for patients with HIV RNA < 50 copies/mL at baseline. J. Arribas, N. Clumeck, M. Nelson, A. Hill, Y. van Delft, C. Moecklinghoff. abstract no. MOPE216, IAS 2011 **(conference abstract)**

MONET trial: methodology as above except this paper reports results at week 144.

Main outcomes:
By Week 144, HIV RNA < 50 copies/mL (ITT, TLOVR, Switch=Failure) was 69% versus 75% in the DRV/r monotherapy and triple therapy arms (difference = -5.9%, 95% C.I. -16.9%, +5.1%); by a switch included analysis, HIV RNA < 50 copies/mL was 84% versus 83.5% (difference = +0.5%, 95% C.I.: -8.7%, +9.7%). 21 and 13 patients had two consecutive HIV RNA results above 50 copies/mL in the DRV/r monotherapy arm and triple therapy arm respectively, of whom 18/21 (86%) and 10/13 (77%) had HIV RNA < 50 copies/mL at Week 144. One patient per arm showed a major IAS-USA PI mutation. HIV RNA at baseline and Hepatitis C co-infection were significantly associated with transient viraemia during the trial (p< 0.05 for each comparison); treatment arm was not

associated with virological failure in any analysis.

Authors' conclusion
In this study for patients with HIV RNA < 50 copies/mL at baseline, switching to DRV/r monotherapy showed non-inferior efficacy to DRV/r + 2NRTI in the switch included analysis, but not in the primary TLOVR switch equals failure analysis.

8. *Fox, J., B. Peters, et al. (2011). "Improvement in vitamin D deficiency following antiretroviral regime change: Results from the MONET trial." AIDS Research & Human Retroviruses 27(1): 29-34.

The aim of this substudy of the MONET trial was to describe the factors associated with vitamin D deficiency at the baseline visit, and investigate the impact of changes in antiretroviral treatment during the trial on changes in vitamin D levels. This is not one of the specified outcomes – exclude.

MONOtherapy Inhibitor protease (MONOI) study performed at 32 Agence Nationale de Recherche sur le SIDA et les Hépatites Virales (ANRS) sites in France (Clinical trial registration NCT00421551)

1. ** Katlama, C., M. A. Valantin, et al. (2010). "Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136." AIDS **24**(15): 2365-2374

Reference	Study type and methodological quality	No pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Katlama, C., M. A. Valantin, et al. (2010). "Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a	**RCT** **Allocation to treatment** Random Method of randomisation: unclear Concealment: adequate	**Total N: 225**	**INCLUSION CRITERIA:** HIV-1-infected pts ≥18 years of age on triple antiretroviral drug regimen; plasma HIV-1 RNA < 400 copies/ml for the past 18 months, based on ≥4 viral load measurements, and < 50 copies/ml at screening; no history of virologic failure while on a protease inhibitor-	**n=112** **Drug(s):** darunavir monotherapy	**n=113** **Drug(s):** triple drug darunavir-containing regimen	**Treatment duration:** 96 weeks **Assessments at:** randomization and at weeks 4, 8	**Primary endpoint:** the proportion of patients with treatment success by week 48 (Treatment failure: virologic failure [2 consecutive	Janssen-Cilag provided darunavir; financial support from Agence Nationale de

randomized open-label, noninferiority trial, MONOI-ANRS 136." AIDS **24**(15): 2365-2374	**Blinding** not blinded **Sample size calculation** stated **ITT analysis** Yes **Setting:** Outpatients		containing regimen; documented CD4 lymphocytes nadir > 50 cells/ml and acceptable laboratory results at screening. First phase: darunavir 600/100 mg twice daily was introduced for 8 weeks as a component of a triple drug regimen instead of the protease inhibitor, NNRTI or third NRTI. Pts whose HIV viral load remained < 50 copies/ml 4 weeks after darunavir induction and who had no severe adverse event or darunavir-related toxicity were included. **EXCLUSION CRITERIA:** Pts with a history of HIV-related neurological disease or with hepatitis B coinfection **Baseline comparability between groups**: yes **Age**: median 45 (IQR 39–56) triple therapy and 46 (IQR 41–51) monotherapy **Gender**: 87 (77%) male triple therapy and 83 (74%) monotherapy **Severity of disease:** median			and every 8 weeks thereafter **Follow-up after end of treatment:** none	measurements of HIV-1 RNA >400 copies/ml within 2 weeks]; treatment modification [any] or discontinuation; withdrawal; pts with a single value of HIV-1 RNA > 400 copies/ ml and a missing second HIV-1 RNA measurement. Other endpoints: proportion of pts with HIV-1 RNA level < 50 copies/ ml and < 400 copies/ ml at each study visit, changes in CD4 cell count and emergence of resistance mutations. For these secondary endpoints, missing data due to missed	Recherche sur le SIDA et les Hépatites Virales, Paris, France (ANRS-MONOI ANRS 136 trial)).

			CD4 cells at baseline 582 (IQR 390–780) triple therapy and 585 (457–757) monotherapy **Duration of disease**: median 8.9 (IQR 4.2–15.6) years triple therapy and 11.7 (6.5–15.9) monotherapy **Duration of ART:** median 7.8 (IQR 3.0–11.3) years triple therapy and 8.7 (4.6–11.3) monotherapy				evaluations were ignored.	

Main outcomes:

48 weeks	Darunavir/r triple therapy	Darunavir/r monotherapy	Difference (%) 90% Confidence interval
Therapeutic success (PP)	101/102 (99.0%)	96/102 (94.1%)	-4.9 (-9.1 to -0.8)
Therapeutic success (ITT)	104/113 (92.0%)	98/112 (87.5%)	-4.5 (-11.2 to +2.1)

Other outcomes:

HIV-1 RNA response to treatment.

	Darunavir/r triple therapy	Darunavir/r monotherapy	Difference 95%	Confidence interval
All HIV-1 RNA <50 copies/ml (PP)	82/102 (80.4)	75/102 (73.5)	-6.86	-18.4 to +4.7
All HIV-1 RNA <50 copies/ml (ITT)	91/113 (80.5)	82/112 (73.2)	-7.32	-18.3 to +3.7

	Monotherapy arm (n=112):	Triple therapy (n=113):
Protocol defined treatment failures:	11	9
confirmed HIV RNA elevations	3*	0
adverse events	4	5
pregnancy	1	0
other reasons	3	1
withdrew consent	3	3

*1 low adherence to therapy; 1had a viral load at week 24 of 411 copies/ml with an adequate darunavir trough concentration of 3480 ng/ml; 1 had discontinued therapy at week 32 with a viral load of 484,569 copies/ml; all 3 patients resuppressed HIV-1 RNA after the addition of two NRTIs. From the three observed virologic failures, one patient had the V11I mutation at failure, but the mutation was also found retrospectively in a previous sample 7 years prior to study entry. No darunavir resistance-associated mutations were found in the other two patients at failure. No darunavir

resistance mutations were also found in the 13 other patients having two consecutive plasma HIV-1 RNA more than 50 copies/ml (11 in the darunavir/r monotherapy group and two in the darunavir/r triple therapy).
At week 48, the median CD4 cell count was 574 cells/ml [interquartile range (IQR) 452–825, median increase 36 cells/ml, IQR-71 to +100] on darunavir/r triple therapy and 621 cells/ml (IQR 481–778, median increase 6 cells/ml, IQR -53 to +93) on darunavir/r monotherapy (P=0.58 by the Wilcoxon rank-sum test).

Adverse events:

	Darunavir/r monotherapy N=112	Darunavir/r triple therapy N=113
Treatment-limiting event, n (%):		
CNS disorders	2 (2%)	0
Hepatic aminotransferase >5 times ULN	0	1 (1%)
Lipodystrophy	1 (1%)	1 (1%)
Hyperglycemia	1 (1%)	0
Hypertriglyceridemia	0	1 (1%)
Diarrhoea	0	1 (1%)
Asthenia	0	1 (1%)
Grade 3 or 4 clinical event:		
Any new sign or symptom	13 (12%)	11 (10%)
Infectious disease events	3 (3%)	2 (2%)
Cardiovascular events	1 (1%)	2 (2%)
Grade 3 or 4 laboratory abnormality:		
Hepatic aminotransferase >5 times ULN	1 (1%)	2 (2%)
Creatine kinase >5 times ULN	0	1 (1%)
Fasting triglycerides >750 mg/dl	1 (1%)	0
Fasting cholesterol >400 mg/dl	0	1 (1%)

Authors' conclusion
Darunavir/r monotherapy exhibited efficacy rate over 85% with concordant results in the magnitude of difference with darunavir/r triple drug regimen in both intent-to-treat and per protocol analyses, but discordant conclusions with respect to the noninferiority margin. Patients failing on darunavir/r monotherapy had no emergence of new darunavir resistance mutations preserving future treatment options.

OK Pilot study

1. ** Arribas J et al (2005). Lopinavir/r as single drug therapy for maintenance of HIV-1 viral suppression. 48-week results of a randomised controlled open label proof of concept pilot clinical trial (OK study) JAIDS 2005, 40: 280-287.

Reference	Study type/ methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Arribas J et al (2005). Lopinavir/r as single drug therapy for maintenance of HIV-1 viral suppression. 48-week results of a randomised controlled open label proof of concept pilot clinical trial (OK study) JAIDS 2005, 40: 280-287.	**RCT** **Allocation to treatment** Random Method of randomisation: adequate (computer-generated) Concealment: adequate **Blinding** not blinded **Sample size calculation** pilot trial: 21 patients per arm the study had a statistical power of 80% to detect a 41% difference between treatment arms **ITT analysis** Yes **Setting:**	**Total N: 42**	**INCLUSION CRITERIA:** at least 18 years old, no history of virologic failure while receiving a protease inhibitor, receiving 2 NRTIs (or tenofovir and 1 nucleoside) and lopinavir/r (400/100 mg b.i.d.) for at least 4 weeks, had had <50 copies of HIV RNA/mL for at least the prior 6 months. **EXCLUSION CRITERIA:** pregnancy, serum hepatitis B surface antigen, need for treatment with agents known to have potential major interactions with lopinavir/r, major psychiatric disease. **Baseline comparability between groups**: yes **Age**: median 42 (range 25-54) years **Gender**: 17 (81%) male on monotherapy and 18 (86%) male on triple therapy	**n=21** **Drug(s):** lopinavir/r (400/100 mg b.i.d.)	**n=21** **Drug(s):** 2 NRTIs (or tenofovir and 1 nucleoside).	**Treatment duration:** **Assessments at:** baseline, 1, 2, 4, 8, 12, 16, and 24 weeks and every 12 weeks thereafter until week 48.	**Primary endpoint:** proportion of pts with <500 copies/mL of HIV RNA of plasma at 48 weeks. Secondary efficacy outcomes: proportion of pts with <50 copies/mL of HIV RNA at week 48, time to loss of virologic suppression through week 48, HIV resistance, changes in the CD4 cell count, frequency and severity of treatment-related adverse events, incidence of laboratory abnormalities, changes in clinical	Abbott Laboratories

	Outpatients		**Severity of disease:** median CD4 cells/µl: 662 (IQR 446–740) on monotherapy and 585 (331–721) on triple therapy				and laboratory values	

Main outcomes/Effect Size:

In an intent-to-treat analysis, with missing HIV RNA level values or change in randomized therapy considered to be >500 copies/mL, 81% (17/21, 95% CI: 64% to 98%) of the patients in the monotherapy group and 95% (20/21, 95% CI: 86% to 100%) of the patients in the triple-therapy group maintained an HIV RNA level of <500 copies/mL at week 48 (P = 0.34; Fisher exact test).

Other outcomes:
All patients who had an HIV RNA level of <500 copies/mL at week 48 were also below detection limit using the <50-copies/mL cutoff. The 95% CI for the difference in response rates at week 48 was -33.4% to +4.9%.
At 72 weeks, percent of patients <50 copies/mL (intention to treat) were 81% (monotherapy arm) and 90.5% (triple-therapy arm). The 95% CI for this difference in response rates at week 72 was -30.5% to +11.4%.

At week 48:	Monotherapy arm (n=21):	Triple therapy (n=21):
Discontinuation due to noncompliance	1	0
Discontinuation due to adverse event	0	1 (hyperlipidemia not responding to lipid-lowering drugs)
Loss of virologic suppression	3 (nucleosides were added back)	0

In patients with loss of virologic suppression after starting lopinavir/r monotherapy, development of primary or active site mutations in the protease was not detected by standard genotyping.

No significant change in CD4 cell count was seen in any group from baseline to week 48. The mean increase from baseline in CD4 cell counts at week 48 was 70 cells/mL for the monotherapy group and 8 cells/mL for the triple-therapy group (P = 0.36; Mann–Whitney U test).

Adverse events:

	Darunavir/r monotherapy N=21	Darunavir/r triple therapy N=21
Grade 3 hypertriglyceridemia	0	1
Grade 3 hypercholesterolemia	1	1

Authors' conclusion
Most of the patients maintained with lopinavir/ritonavir monotherapy remain with undetectable viral load after 48 weeks. Failures of lopinavir/ritonavir monotherapy were not associated with the development of primary resistance mutations in the protease gene and could be successfully reinduced adding back prior nucleosides.

2. *Pulido, F., R. Delgado, et al. (2008). "Long-term (4 years) efficacy of lopinavir/ritonavir monotherapy for maintenance of HIV suppression." Journal of Antimicrobial Chemotherapy **61**(6): 1359-1361. (comment: long term FU of OK and OK4 trials of PI monotherapy arm – cohort analysis)
Long-term cohort follow up of the 21 patients in the Arribas 2005 OK pilot trial (exclude – no comparator)

OK04 study

1. ** Pulido, F., J. R. Arribas, et al. (2008). "Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and two nucleosides for maintenance therapy of HIV." AIDS **22**(2): F1-9.

Reference	**Study type and methodological quality**	**No. pts**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Pulido, F., J. R. Arribas, et al. (2008). "Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and two nucleosides for maintenance therapy	**RCT** **Allocation to treatment** Random Method of randomisation: adequate (computer-generated) Concealment: adequate **Blinding** not blinded **Sample size**	**Total N: 205**	**INCLUSION CRITERIA** at least 18 years old, no previous suspected or confirmed virological failure while receiving a protease inhibitor, receiving two nucleoside reverse transcriptase inhibitors (or one nucleoside plus tenofovir DF) and lopinavir-ritonavir soft gel capsule (400/100 mg bid) for at least 4 weeks and had <50 copies of HIV RNA/mL for at least the	**n=103** **Drug(s):** LPV/r	**n=102** **Drug(s):** LPV/r + 2 NRTIs	**Treatment duration:** **Assessments at:** at baseline, week 4, week 12, and every 12 weeks thereafter until week 48 **Follow-up**	**Primary endpoint:** proportion of pts without therapeutic failure at 48 weeks, defined as any of: i) 2 consecutive measurements of HIV RNA >500 copies/mL separated by at least 2 weeks [pts on monotherapy who failed by this definition were not considered therapeutic failures if at the time of failure there was no evidence of lopinavir-ritonavir genotypic	Abbott Laboratories and the Fundación de Investigación Médica Mutua Madrileña (MUTUA 2005-066).

of HIV." AIDS **22**(2): F1-9.	**calculation** stated **ITT analysis** Yes **Setting:** Outpatients		prior 6 months. Pts with a single transitory episode of detectable viral load ('blip', defined as an HIV RNA viral load >50 copies/mL preceded and followed by one HIV-RNA viral load <50 copies/mL without changes in antireteroviral treatment) during the prior 6 months could also been included. **EXCLUSION CRITERIA:** pregnancy, serum hepatitis B surface antigen in pts treated with lamivudine, emtricitabine or tenofovir DF, need for treatment with agents known to have potential major interactions with lopinavir-ritonavir, major psychiatric disease **Baseline comparability between groups**: yes **Age**: median 41 (range 28-78) years on monotherapy and 42 (26-65) years on triple therapy **Gender**: 79 (78%) male on monotherapy and 84 (82%) on triple therapy			**after end of treatment:**	resistance, were reinduced with two nucleosides and were suppressed to <50 copies/mL of HIV RNA at 48 weeks]; (ii) change of randomized therapy for reasons different from re-induction in the monotherapy group; (iii) treatment discontinuation; (iv) loss to follow-up; (v) for patients re-induced in the monotherapy group: decrease in HIV RNA <1 log_{10} 4 weeks after reinduction or failure to reach HIV RNA <50 copies/mL 16 weeks after reinduction)**.** Other endpoints: proportion of pts with virological failure (HIV RNA >50 or >500 copies/ mL, according to the analysis) through week 48. Missing data, early termination of participation in the study, or re-induction with nucleosides in the monotherapy group were considered to be failures in these analyses. Also	

			Severity of disease: median CD4 cells per µl: 474 (IQR 340–660) on monotherapy and 473 (307–673) on triple therapy				development of HIV resistance and changes in the CD4 cell count.	

Main outcomes:

At week 48:	Monotherapy arm (n=103):	Triple therapy (n=102):
Randomised but not dosed	3	4
Discontinuations	4 (3 loss to follow-up, 1 change of therapy)	7 (3 adverse events, 4 loss to follow-up)
Loss of virologic suppression (per protocol analysis)	6/100 (2 therapeutic failure [1 resistance, 1 did not maintain virological suppression after resuming baseline nucleosides]; 4 resuppressions on NRTIs)	3/98
ITT analysis (missing HIV RNA level values or change in randomized therapy, including successful reinduction with nucleosides in the monotherapy group, were considered to be failures)	85% not failures (85/100)	90% not failures (88/98)
If those randomised but not dosed considered failures:	82.5% (85/103)	88.2% (90/102)

Other outcomes:
The mean increase from baseline in CD4 cell counts at week 48 was 65 cells/mL for the monotherapy group and 31cells/mL for the triple therapy group (P=0.31; Mann- Whitney U test).

Study drug-related adverse events of at least moderate severity occurred in three patients in the triple therapy group (3%) and none (0%) in the monotherapy group (P=0.08). The three adverse events in the triple therapy group were diarrhoea (two patients) and insomnia. These three adverse events resulted in treatment discontinuation.

At week 48:	Monotherapy arm (n=103):	Triple therapy (n=102):
Grade 3 or 4 hypertriglyceridaemia	3	3
Grade 3 or 4 hypercholesterolemia	10	4
Grade 3 or 4 aspartate aminotransferase (AST) or alanine aminotransferase (ALT)	4	2

elevations (5 of the 6 pts were coinfected with hepatitis C virus)		

In both treatment groups there were no statistically significant changes from baseline in fasting total cholesterol, high-density lipoprotein cholesterol or triglycerides. No patient discontinued the study because of elevated lipid or aminotransferase levels.

There were 15 patients (11 in the monotherapy group, four in the triple therapy group) who qualified for genotypic testing due to a HIV RNA >500 HIV RNA copies/mL. Protease inhibitor associated mutations were detected in three subjects, two (2%) in the monotherapy group, and one (1%), in the triple group (P=0.56; Fisher exact test). All three subjects had exhibited more than one episode of viraemia >500 copies/mL. Reverse transcriptase mutations were detected in two subjects, one in the monotherapy group and one in the triple therapy group.

Authors' conclusion
48 weeks of lopinavir-ritonavir monotherapy with reintroduction of nucleosides as needed was non-inferior to continuation of two nucleosides and lopinavir-ritonavir in patients with prior stable suppression. However, episodes of low level viremia were more common in patients receiving monotherapy.

2. ** Arribas, J. R., R. Delgado, et al. (2009). "Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and 2 nucleosides for maintenance therapy of HIV: 96-week analysis." Journal of Acquired Immune Deficiency Syndromes: JAIDS **51**(2): 147-152.

Reference: Arribas, J. R., R. Delgado, et al. (2009). "Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and 2 nucleosides for maintenance therapy of HIV: 96-week analysis." Journal of Acquired Immune Deficiency Syndromes: JAIDS **51**(2): 147-152.

OK04 trial: methodology as above except 96 week outcomes (not analysed again as double counting)

Main outcomes/Effect Size:

At week 96: (Only Patients Randomized and Dosed)	Monotherapy arm (n=100):	Triple therapy (n=98):
Still receiving randomized therapy	77	76
Therapeutic failure	13	22
Loss of virologic control (confirmed HIV RNA >500 copies/mL)	6	5
Reinduction with nucleosides due to HIV RNA >500 copies/mL	5	NA
Reinduction with nucleosides due to HIV RNA >50 HIV RNA copies/mL but <500 copies/mL	7	NA
Lost to follow-up	8	9

Death (Myocardial infarction after cocaine use, with HIV RNA <50 copies per millilitre)	1	0
Change in randomized treatment (not due to reinduction)	1	0
Discontinuation due to adverse events	0	8 (p = 0.003)

By an intention to treat analysis in which missing data and reinduction with nucleosides are considered failures, 77.6% (76 of 98) of patients receiving triple therapy had an HIV RNA <50 copies per milliliter compared with 77% (77 of 100) of patients receiving monotherapy (P = 0.865; log rank). At week 96, by observed treatment analysis in which missing data or change in therapy is censored and reinduction with nucleosides is considered failure, 94.4% of patients receiving triple therapy had an HIV RNA <50 copies per milliliter compared with 86.4% of patients receiving monotherapy (P = 0.06; log rank).

At week 96, proportion of patients without therapeutic failure according to our primary end point definition (for which the 10 patients with successful reinductions are not considered failures) was 78% in the triple therapy group and 87% in the monotherapy group (difference: 29%; 95% CI: 220% to +1.2%, P = 0.09). The upper limit of the CI for the difference (+1.2%) fulfilled the preestablished criteria for noninferiority of the monotherapy group.

Other outcomes:
The mean increase from baseline in CD4 cell counts at week 96 was 71 cells per microliter in the monotherapy group and 47 cells per microliter in the triple therapy group (difference not statistically significant).

In total, after 2 years of follow-up, proportion of patients rebounding with isolates containing major protease inhibitor mutations was 2% in the monotherapy group and 2% in the triple therapy group.

At week 96, 8 patients had discontinued randomized therapy due to adverse events in the triple therapy group vs. none in the monotherapy group (P = 0.003).

In both treatment groups, there were no statistically significant changes from baseline in fasting total cholesterol, high-density lipoprotein cholesterol, or triglycerides. No patient discontinued the study because of elevated lipid or aminotransferase levels.

At week 96:	Monotherapy arm (n=100):	Triple therapy (n=98):
Grade 3 or 4 hypertriglyceridaemia	8	6
Grade 3 or 4 hypercholesterolemia	11	7
Grade 3 or 4 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations (10 of the 11 pts were coinfected with hepatitis C virus)	7	4

Authors' conclusion
The 96 week results of the OK04 trial continue to support the efficacy and safety of the lopinavir–ritonavir monotherapy strategy. Although episodes of low-level viremia were more frequent in the monotherapy group, we did not observe an increased risk of resistance development and most of these patients could be resuppressed restarting nucleosides. The toxicity of the monotherapy regimen was lower than the toxicity of the triple regimen.

3. *Pulido, F., I. Perez-Valero, et al. (2009). "Risk factors for loss of virological suppression in patients receiving lopinavir/ritonavir monotherapy for maintenance of HIV suppression." Antiviral Therapy **14**(2): 195-201
   Exclude – this is looking at the cohort of 121 patients on monotherapy in OK and OK04 studies and correlating risk factors for risk of suppression (no comparator)

4. * F. Pulido, J. Arribas and OK04 Study Group. No effect of HCV infection on virological response 96 weeks after simplification to lopinavir/ritonavir (LPV/r) monotherapy (MT) in the OK04 trial. MOPE217. 6th IAS Conference. 17th-20thJuly2011. Rome. Italy (Conference abstract)

Reference: F. Pulido, J. Arribas and OK04 Study Group. No effect of HCV infection on virological response 96 weeks after simplification to lopinavir/ritonavir (LPV/r) monotherapy (MT) in the OK04 trial. MOPE217. 6th IAS Conference. 17th-20thJuly2011. Rome. Italy (Conference abstract)

OK04 trial: methodology as above except this paper assessed the impact of baseline anti-HCV+ on 96 week outcomes in the OK04 study (i.e. sub-group analysis; not analysed again).

Main outcomes/Effect Size:

HIV-RNA <50 copies/mL, missing data or change of therapy = failure [M/C=F]: monotherapy HCV+: 70.5% (n=44), HCV-: 82.1% (n=56), p=0.23; triple therapy HCV+: 74% (n=50), HCV-: 81.3% (n=48), p=0.47
HIV-RNA <50 copies/ml, missing data or change of therapy for reasons other than virological failure are censored [Virological failure (VF)]: monotherapy HCV+: 90.9% (n=44), HCV-: 83.9% (n=56), p=0.38; triple therapy HCV+: 94% (n=50), HCV-: 95.8% (n=48), p=1.0.

Authors' conclusion
In the OK04 trial, patients with anti-HCV+ at baseline on LPV/r MT did not have higher rates of virological failure than anti-HCV-patients.

5. *McKinnon, J. E., R. Delgado, et al. (2011). "Single genome sequencing of HIV-1 gag protease resistance mutations at virologic failure during the OK04 trial of simplified versus standard maintenance therapy." Antiviral Therapy 16(5): 725-732.

Reference: McKinnon, J. E., R. Delgado, et al. (2011). "Single genome sequencing of HIV-1 gag protease resistance mutations at virologic failure during the OK04 trial of simplified versus standard maintenance therapy." Antiviral Therapy **16**(5): 725-732. OK04 study: In this paper, the authors report developing a single genome sequencing (SGS) assay of HIV-1 gag and protease to assess the emergence of low-frequency drug-resistant variants during virological rebound.
Main outcomes/Effect Size: Major protease resistance mutations: 3/11 monotherapy and 3/4 triple therapy; median number of minor protease resistance mutations 3.0 monotherapy and 3.5 triple therapy. **Authors' conclusion** Although more subjects on monotherapy had virological rebound, this was not associated with more frequent emergence of variants encoding PI resistance mutations in gag or protease detected by SGS.

Cahn study (NCT00159224):

Cahn, P., J. Montaner, et al. (2011). "Pilot, Randomized Study Assessing Safety, Tolerability and Efficacy of Simplified LPV/r Maintenance Therapy in HIV Patients on the 1 PI-Based Regimen." PLoS ONE [Electronic Resource] **6(8): e23726. ClinicalTrials.gov NCT00159224

Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Cahn, P., J. Montaner, et al. (2011). "Pilot, Randomized Study	**RCT** **Allocation to treatment** Random Method of	**Total N: 80**	**INCLUSION CRITERIA:** HIV-1 infected adults: i) on their first ART regimen, composed of any two NRTIs plus LPV/r or a PI/r combination; and ii) virologically suppressed	**n=41** **Drug(s):** Lopinavir/r 133.3/33.3 mg	**n=39** **Drug(s):** standard HAART regimen	**Treatment duration:** 1 year **Assessme**	**Primary endpoint:** % pts with plasma HIV-1 RNA level <200 copies/ml at Day 360 Other endpoints: %	Abbott Canada

Assessing Safety, Tolerability and Efficacy of Simplified LPV/r Maintenance Therapy in HIV Patients on the 1 PI-Based Regimen." PLoS ONE [Electronic Resource] **6**(8): e23726.	randomisation: adequate Concealment: adequate **Blinding** not blinded **Sample size calculation** stated **ITT analysis** Yes **Setting:** Outpatients		(HIV-1 RNA viral load <50 copies/ml) at least 6 months prior to study entry and a CD4+ T-cell count ≥100 cells/ mm^3. **EXCLUSION CRITERIA:** HBsAg+, active TB or opportunistic infection, active malignancy (except Kaposi's Sarcoma), ALT/AST >5x ULN, uncontrolled substance abuse or psychiatric illness that could preclude compliance with protocol; pregnant or lactating; received an investigational drug within 30 days prior to study initiation; had modified ART within 3 months of study entry or intending to do so during the study **Baseline comparability between groups**: yes **Age**: mean 39 (9.3) years **Gender**: 84% male **Severity of disease:** mean (SD) CD4+ T-cell count and log_{10} HIV-1 RNA 383 (195) cells/mm^3 and 1.68 (0.08) log_{10} copies/ml, respectively	soft gel capsules; 3 capsules BID orally with food		**nts at:** Screening / Baseline (Day -1) and Days 15, 30, 60, 90, 120, 150, 180, 240, 300, and 360. **Follow-up after end of treatment:**	pts with plasma HIV-1 RNA <50 copies/mL at Day 360; time to confirmed virologic rebound (≥200 copies/ml and ≥50 copies/ml) or meeting the criteria for virologic failure (pts with viral load test >50 copies/ml and second viral load >200 copies/ml) through Day 360; mean change in Viral Load and CD4+ T-cell count from baseline to final assessment; impact on patient-reported outcomes (PROs) assessed by Symptoms Distress Module (SDM; higher values indicate worse PROs); treatment emergent adverse events (AE), changes in vital signs and clinical laboratory data, metabolic toxicity	

			Duration of disease: mean (SD) time since initial HIV diagnosis 3.3 (3.0) years					

Main outcomes/Effect Size:
2/41 monotherapy discontinued (adverse event); 7/39 standard therapy discontinued (1 adverse event; 1 protocol violation, 1 virological failure; 3 withdrawal of consent; 1 other)

In an ITT analysis using the LOCF principle, 37 of the 39 patients (95%) in the ST group and 40 of the 41 patients (98%) in the IM group had plasma HIV-1 RNA <200 copies/ml (OR= 0.46; 95% CI: 0.04–5.31; P= 0.611).

Other outcomes:

Patients with plasma HIV-1 RNA <50 copies/ml at 360 days, applying again the LOCF principle, there were 36/39 patients (92%) for the ST and 39/41 (95%) for the IM group (OR =0.61; 95% CI: 0.097–3.897; P =0.671). Four (10%) patients on LPV/r were intensified with 2 NRTIs and all of them regained virologic control, as demonstrated by achieving a plasma HIV-1 RNA <50 copies/mL following the intensification.

For time to first confirmed virologic rebound of ≥200 plasma HIV-1 RNA copies/ml, a hazard ratio (95% CI) of 2.62 (0.26–24.20) for IM versus ST was calculated, which was not statistically significant (P= 0.405). Similarly, the time to first confirmed virologic rebound of ≥50 HIV-1 RNA copies/ml was comparable in the two groups with an estimated hazard ratio (95% CI) of 4.19 (0.90–19.43), P= 0.067.

Parameter	Visit	Standard Therapy		Monotherapy		Total		p value
		N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
Absolute CD4+ T-cell count	Baseline	39	401.2 (222.5)	41	364.6 (164.3)	80	382.5 (194.5)	0.404
	360 days	32	478.6 (246.4)	39	453.8 (249.4)	71	465.0 (246.6)	0.678
	Change	32	56.8 (168.93)	39	89.3 (196.18)	71	74.6 (183.84)	0.463
Viral load log_{10} RNA copies/ml	Baseline	39	1.689 (0.063)	41	1.680 (0.087)	80	1.684 (0.076)	0.592
	360 days	31	1.692 (0.079)	39	1.734 (0.249)	70	1.715 (0.193)	0.369
	Change	31	0.006 (0.032)	39	0.055 (0.245)	70	0.033 (0.184)	0.361

Symptoms Distress Module	Baseline		31.8		31.7			
	360 days		29.6		26.2			
	Change		P =0.094		P= 0.003			P= 0.131

The most frequent adverse events were diarrhoea (19%), headache (18%), influenza (16%), nasopharyngitis (13%), back pain (10%), hypertriglyceremia (8%) and insomnia (8%). Adverse events were predominantly mild in severity and judged unrelated to the study drug. There were three SAEs reported by two patients in the IM group (1 thrombocytopenia, 1 upper abdominal pain and 1 pneumonia) and five SAEs reported by three patients in the ST group, of which seven were considered severe and one in the IM group was moderate. All SAEs were considered unrelated to the study drug.

Authors' conclusion
At day-360, virologic efficacy and safety of LPV/r appears comparable to that of a PI+2NRTIs HAART. These results suggest that our individualized, simplified maintenance strategy with LPV/r-monotherapy and protocol-mandated NRTI re-introduction upon viral rebound, in virologically-suppressed patients merits further prospective long-term evaluation.

Gutmann study (MOST)

1. **Gutmann, C., A. Cusini, et al. (2010). "Randomized controlled study demonstrating failure of LPV/r monotherapy in HIV: the role of compartment and CD4-nadir." AIDS **24**(15): 2347-2354. Monotherapy Switzerland/Thailand study (MOST)

Reference	**Study type and methodological quality**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Gutmann, C., A. Cusini, et al. (2010). "Randomized controlled study demonstrating failure of LPV/r monotherapy in	**RCT** **Allocation to treatment** Random Method of randomisation: unclear	**Total N: 60**	**INCLUSION CRITERIA** HIV patients with fully suppressed viral load **EXCLUSION CRITERIA:** previous history of virologic	**n=29** **Drug(s):** Lopinavir/r 400/100 mg	**n=31** **Drug(s):** triple therapy	**Treatment duration:** 48 weeks **Assessments at:** baseline, then every	**Primary endpoint:** treatment failure in the CNS or genital compartment. As expected HIV RNA levels in the compartments are not fully established,	This study has been financed in the framework of the Swiss HIV Cohort

HIV: the role of compartment and CD4-nadir." AIDS **24**(15): 2347-2354.	Concealment: unclear **Blinding** not blinded **Sample size calculation** Yes. Also, defined study termination criteria in the case of an unexpectedly high degree of treatment failure in blood. Premature study termination was mandated if more than six (20%) of the first 30 patients on monotherapy failed treatment. Failure was defined as two consecutive plasma HIV RNA levels more than 400 cell/ml. **ITT analysis** Yes **Setting:** Outpatients		treatment failure with any drug combination or documented protease inhibitor resistance. **Baseline comparability between groups**: yes **Age**: mean 46+/-11 years standard therapy and 42+/-7 years monotherapy **Gender**: Male: 24 (77%) standard and 19 (66%) monotherapy **Severity of disease:** median CD4 465 (IQR 356–625) standard and 498 (IQR 360–670) monotherapy	twice daily monotherapy		6 weeks to week 24 and every 8 weeks thereafter **Follow-up after end of treatment:** none	compartment failure was defined as an HIV RNA level one log above the respective value at baseline. If baseline values were undetectable, a level of 40cp/ml was assumed. However, as the trial was terminated when recruitment reached 60% of plan, the analysis of primary endpoints was not possible. The focus of investigations therefore shifted to explaining these failures and looking for predictive factors.	Study, supported by the Swiss National Science Foundation (SHCS Project 490) and by a grant of the Swiss National Science Foundation (SNF Grant 3247B0-114006).
Main outcomes/Effect Size: Six patients reached HIV-RNA failing criteria (all on monotherapy). With a median of 4.2 $\log_{10}$ cp/ml, CSF HIVRNA in the five failures who consented to lumbar puncture was higher than the respective level in blood plasma (median 3.4 $\log_{10}$ cp/ml, P=0.15). Five of the six failing patients presented with clinical symptoms at the time of failure: one patient had sialadenitis, four had neurological symptoms such as headache, dizziness, visual disturbance, deficit in concentration and ataxic gait. There was no history of previous neurological symptoms in all four failing patients. None of the other patients during the trial presented with signs or symptoms of acute neurological discomfort. In all failing								

patients, viral RNA was completely resuppressed after switching to previous triple therapy.

Genotypic resistance testing performed in CSF and in plasma of the failing patients did not reveal any mutation associated with drug either in the protease or in the reverse transcriptase region. All clinical findings, especially CNS symptoms, resolved completely after treatment switch.

Cerebrospinal fluid was examined in all 60 patients at baseline and in 45 patients at study termination (25 monotherapy with blood viral load <400, five failing monotherapy, 15 continued treatment patients with blood viral load <50). At baseline, three patients had low level HIV-RNA in CSF (82, 56, and 43 cp/ml). Two of the three were randomized to continuous therapy [efavirenz+TDF+3TC and TDF+FTC+atazanavir, ritonavir-boosted (ATV/r)] and both had undetectable HIV-RNA in CSF and blood at study termination. The third patient with 1.6 $\log_{10}$ (43) cp/ml, was randomized to monotherapy. At week 37, when the study was prematurely terminated, his viral load in CSF was 2.4 $\log_{10}$ (250) cp/ml, whereas blood viral load was undetectable. One additional patient on triple therapy had a detectable viral load in CSF of 1.6 $\log_{10}$ (45) cp/ml at week 48, whereas plasma viral load was undetectable. At this time, he was switched from TDF+FTC+ATV/r to monotherapy. Eighteen weeks later, at the termination visit, viral load in CSF was 3.4 $\log_{10}$ (2300) cp/ml, whereas viral load in plasma was 2.2 $\log_{10}$ (170) cp/ml.

Among all non-failing patients (viral load <400) at study termination, none of the 15 patients still under continued treatment had an HIV-RNA value in CSF more than 1.6 $\log_{10}$ (40) cp/ml, as opposed to eight of 25 monotherapy patients (32%, P¼0.01, Fisher's exact). Only four of the eight did reach the predefined CSF-failing criteria (>2.6 $\log_{10}$ cp/ml). Interestingly, three of the four CSF-failures had a plasma HIV-RNA value between 1.6 and 2.6 $\log_{10}$ (40–400) cp/ml. In all four patients, HIV RNA was more than one log higher in CSF than in blood. Mean CD4 nadir in cases with isolated CSF failures was not significantly different than in the monotherapy patients who had undetectable HIV-RNA in CSF at termination; 171/ml (IQR 123–251) vs. 211/ml (IQR 168–272), P=0.28.

Only patients on monotherapy (≥6 weeks, n=42) were included in the analysis of risk factors for treatment failure (n=6). In univariate analysis, the following parameters were not associated with treatment failure in blood: age, sex, therapy prior to baseline and duration of HIV-RNA suppression less than 50 cp/ml, CDC classification, RNA set point, hepatitis C virus coinfection, length of therapy, peripheral blood mononuclear cell-associated HIV-DNA and RNA, hemoglobin and platelets. Cholesterol showed a trend for lower baseline cholesterol (t-test; P=0.053), with failures having lower baseline cholesterol levels compared with nonfailures (4.5+/-0.7 vs. 5.3+/-1.1). Median nadir CD4 cell count in failing patients was 56/ml (IQR 19-126) vs. 194/ml (IQR 99-257) in nonfailing patients (P=0.026; Mann–Whitney-U). Similarly, median baseline CD4 cell count was 335/ml (IQR 301–373) vs. 554/ml (IQR 413–720, P=0.019; Mann– Whitney-U). Cox regression analysis revealed a significant difference between the number of failures in patients with low (<200/ml) and high CD4 nadir (P<0.01). No monotherapy failure occurred in patients with nadir CD4 cell count more than 200 cells/ml.

Evaluation of frequency of blips as a proxy for decreased potency of monotherapy showed that low level rebound (40–400 cp/ml) was significantly more frequent in the monotherapy arm (8 vs. 2% with HIV RNA 40–400 cp/ ml under monotherapy vs. continued treatment among 191 vs. 210 RNA determinations per group; P<0.01. No significant difference in changes in CD4 cell count was detectable between the monotherapy and continued

treatment arms.

Results of HIV-RNA determination in the genital tract showed no marked elevation of HIV-RNA in the genital secretions. Neuropsychological tests demonstrated no significant changes.

Authors' conclusion
Maintenance of HIV therapy with LPV/r alone should not be recommended as a standard strategy; particularly not in patients with a CD4 cell count nadir less than 200/ml. Further studies are warranted to elucidate the role of the central nervous system compartment in monotherapy-failure.

KALESOLO Trial

1. **Meynard, J.-L., V. Bouteloup, et al. (2010). "Lopinavir/ritonavir monotherapy versus current treatment continuation for maintenance therapy of HIV-1 infection: the KALESOLO trial." Journal of Antimicrobial Chemotherapy **65**(11): 2436-2444. NCT00140751

Reference	**Study type and methodological quality**	**No. pts**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Meynard, J.-L., V. Bouteloup, et al. (2010). "Lopinavir/ ritonavir monotherapy versus current treatment continuation for maintenance therapy of HIV-1 infection: the	**RCT** **Allocation to treatment** Random Method of randomisation: adequate Concealment: adequate **Blinding** not blinded **Sample size calculation**	**Total N: 186**	**INCLUSION CRITERIA** HIV-1 infection; age >18 years; no previous history of virological failure on a PI; HIV-1 RNA <50 copies/mL for at least 6 months; no change in antiretroviral treatment in last 3 months; no opportunistic	**n=87** **Drug(s):** lopinavir/ ritonavir monotherapy (400/100 mg twice a day)	**n=99** **Drug(s):** continue current cART	**Treatment duration:** 48 weeks **Assessments at:** screening/ baseline and every 12 week period thereafter for 48 weeks	**Primary endpoint:** % pts with viral load <50 copies/mL at week 48 without modification of antiretroviral treatment during the study. Modifications of treatment included any change except dosing adaptation or replacement by a fixed combination. Pts lost to follow-up or with no HIV-1 RNA	Institut de Médecine et d'Epidémiologie Appliquée (IMEA), Paris.

KALESOLO trial." Journal of Antimicrobial Chemotherapy **65**(11): 2436-2444.	stated **ITT analysis** Yes **Setting:** Outpatients		infection in the last 6 months. Patients with triple NRTI regimen could be included. **EXCLUSION CRITERIA:** pregnancy; hepatitis B treated with lamivudine or tenofovir DF **Baseline comparability between groups**: yes **Age**: median 43 (IQR 39–50) combination therapy and 44 (39–51) monotherapy **Gender**: male: 75 (76%) combination and 63 (72%) monotherapy **Severity of diease:** median CD4 cell count 525 (IQR 357–688) combination and 494 (371–630) monotherapy			**Follow-up after end of treatment:** at week 96 (only subset of patients followed up)	measurement at Week 48 were considered as failures (missing= failure) Other endpoints: % pts with viral load <400 copies/mL at Week 48 without modification of antiretroviral treatment during the study, % pts with viral load <50 copies/mL at Week 48 with treatment intensification not considered as failure. Success with treatment intensification allowed was defined in lopinavir/ ritonavir monotherapy group by a viral load <50 copies/mL at Week 48 even if NRTIs had been reintroduced; in the current cART group, success was defined by a viral load of <50 copies/mL at Week 48 without change of treatment. Variation in CD4 cell count, evolution of biological	

			Duration of disease: median duration since HIV-1 infection 10 years				parameters, evolution of DEXA scan parameters, treatment adherence, clinical and biological safety.	

Main outcomes/Effect Size:

At Week 48, 73/87 patients (84%) in the lopinavir/ritonavir monotherapy group were virologically suppressed to <50 copies/mL for the primary endpoint compared with 87/99 patients (88%) in the current cART group. The percentage difference between the two groups was -4.0% with a 90% two-sided CI -12.4% to +4.5%. Non-inferiority was therefore not demonstrated on the primary outcome.

	lopinavir/ritonavir monotherapy	current cART
Therapeutic failure:	14/87	12/99
Plasma HIV-1 RNA was ≥50 copies/mL	5	0
Missing RNA value	0	5
Changed their regimen during the trial	9 (clinician's assessment virological failure 8 + 1 adverse events [dyslipidaemia])	7 (lipodystrophy, n=1; altered renal function, n=2; and unspecified, n=4)

If antiretroviral treatment intensification was taken into account to evaluate therapeutic success at Week 48 (plasma HIV-1 RNA <50 copies/mL, addition of NRTIs allowed in lopinavir/ ritonavir monotherapy group), the proportions of patients meeting the primary endpoint were 87/99 (88%) in the current cART group and 79/87 (91%) in the lopinavir/ritonavir monotherapy group (difference, 2.9; 90% CI, -4.5 to +10.4).

Other outcomes:

In the current cART group, median CD4 counts increased from 525 to 604 cells/mm3 between baseline and Week 48 and in the lopinavir/ritonavir monotherapy group, from 494 to 592 cells/mm^3.

Failures of lopinavir/ritonavir monotherapy did not show acquired resistance mutations in the protease gene.

Changes from inclusion to Week 48 in fasting triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol and creatinine clearance were assessed. The only difference between treatment groups was fasting total cholesterol change, which was significantly higher in the lopinavir/ritonavir monotherapy group (+0.42 mmol/L) than in the current cART group (+0.08 mmol/L; P=0.04).

Seventy patients were included in a DEXA substudy (not data extracted).

	lopinavir/ritonavir monotherapy	current cART
Grade 3–4 biological events	3 (total cholesterol increase, n=1; serum alanine aminotransferase (ALT) increase, n=1; serum aspartate aminotransferase (AST) and ALT increase, n=1; the increase in serum AST and ALT was related to acute hepatitis C).	3 (total cholesterol and triglycerides increase, n=1; triglycerides increase, n=2)

Thirteen patients in the current cART group experienced at least one episode of diarrhoea versus 34 in the lopinavir/ritonavir group (P<0.001).

Authors' conclusion
Lopinavir/ritonavir monotherapy did not achieve non-inferiority versus cART for maintaining plasma HIV-1 RNA at <50 copies/mL. Nevertheless, the incidence of virological failure was low (mostly with HIV-1 RNA <400 copies/mL) and easily managed by treatment intensification.

KalMo Study

1. **Nunes, E. P., M. Santini de Oliveira, et al. (2009). "Monotherapy with Lopinavir/Ritonavir as maintenance after HIV-1 viral suppression: results of a 96-week randomized, controlled, open-label, pilot trial (KalMo study)." HIV Clinical Trials **10**(6): 368-374.

Reference	**Study type and methodological quality**	**No. pts**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Nunes, E. P., M. Santini de Oliveira, et al. (2009). "Monotherapy with Lopinavir/ Ritonavir as maintenance after HIV-1 viral suppression: results of a 96-week randomized,	**RCT** **Allocation to treatment** Random Method of randomisation: adequate Concealment: adequate **Blinding** not blinded **Sample size**	**Total N: 60**	**INCLUSION CRITERIA** HIV-1 infected, ≥18 years, virologic suppression <80 copies/mm3 (lower limit of Nucleic Acid Sequence Based Amplification [NASBA] assay, most widely available at that time in Brazil), on a stable HAART regimen for at least 6 months, CD4 levels >200 cells/mm^3 at screening, and CD4 nadir	**n=30** **Drug(s):** lopinavir/r monotherapy 400 + 100 mg bid	**n=30** **Drug(s):** maintain current HAART regimen	**Treatment duration:** 96 weeks **Assessments at:** baseline and at Weeks 2, 4, and 12, and then every 12 weeks until Week	**Primary endpoint:** proportion of patients with PVL <80 copies/mL of HIV RNA at Week 96 on intention-to-treat (ITT) analysis with all missing data counting as failure Other endpoints: VF was defined as two consecutive	partially supported by Abbott Laboratories

controlled, open-label, pilot trial (KalMo study)." HIV Clinical Trials **10**(6): 368-374.	**calculation** not stated **ITT analysis** Yes **Setting:** Outpatients		> 100 cells/mm^3. **EXCLUSION CRITERIA:** Pregnant or breastfeeding women; previous history of an AIDS-defining condition, virologic failure, or intolerance to lopinavir **Baseline comparability between groups**: yes **Age**: median 39 (IQR 31–46) monotherapy and 40 (31–46) current cART **Gender**: male: 17 (54.8%) monotherapy and 20 (69.0%) current cART **Severity of disease:** CD4 count: median 538 (IQR 365–738) monotherapy and 510 (355–608) current cART			96. **Follow-up after end of treatment:** none	measures of HIV-1 PVL >500 copies/mL within an interval of 4 (±1) weeks. Incidence of AIDS-defining illnesses; CD4 cells count changes during the study period; and incidence of antiretroviral-related clinical and laboratory adverse events including changes in anthropometric measures and lipids profile.	

Main outcomes/Effect Size:

At Week 96, by ITT analysis, 26/30 (86.7%; 95% CI, 74.5–98.8) and 24/30 (80.0%; 95% CI, 65.7–94.3) subjects in the control and monotherapy arms remained virologically suppressed (*p* = .48).

	lopinavir/ritonavir monotherapy	current cART
Discontinuations:	6	3
virological failure	1 (no resistance; successfully resuppressed)	1 (no resistance)
grade 3 diarrhea	1	0
lost to follow-up	1	0
pregnancy	2	1

tuberculosis	1	0
imprisonment	0	1

On-treatment analysis including only patients who completed 96 weeks of follow-up without discontinuation for reasons other than VF showed 96% efficacy in both groups (24/25 patients in the monotherapy group and 26/27 patients in the control group).

Other outcomes:
At Week 96, no statistically significant differences in median CD4 count changes were observed between the control and the monotherapy arms (42 [IQR 35 to 133] and 91 [IQR −55 to 169], respectively; *p* = .93). No AIDS-defining conditions occurred during the study period. One case of tuberculosis in the monotherapy group was not considered to be associated with immunosuppression, because it was a localized presentation (vertebral tuberculosis); at the last visit before this diagnosis, the patient did not show a significant decrease in CD4 count or loss of virologic suppression.

More patients in the monotherapy arm experienced gastrointestinal side effects (24 vs. 10 in monotherapy and maintenance arms, respectively; *p* = .001), including one study discontinuation due to diarrhoea. No other statistically significant differences were detected between the two study arms. In the control arm, five subjects had their regimen changed due to drug-related toxicities, three patients switched from stavudine to tenofovir, one patient switched from indinavir to atazanavir, and one patient switched from didanosine to lamivudine.

	lopinavir/ritonavir monotherapy	current cART
Grade 3–4 abnormality of triglycerides	0	2
Grade 3 abnormalities of cholesterol	2	3

No other clinically significant laboratory abnormalities of grades 3 or 4 were observed in any of the study groups.

Authors' conclusion
Switching from various HAART regimens to LPV/r monotherapy in patients who were virologically suppressed and without a history of previous virologic failure was effective, safe, and well tolerated through 96 weeks.

KAMON 2

H. Hasson, L. Galli, G. Gallotta, V. Neri, P. Blanc, M. D'Annunzio, G. Morsica, S. Bagaglio, S. Sollima, A. Lazzarin, C. Uberti Foppa. HAART simplification with lopinavir/ ritonavir monotherapy in HIV/HCV coinfected patients starting anti-HCV treatment: final results of a randomised, proof-of-principle clinical trial (KAMON 2 Study) IAS 2011: abstract no. CDB358 **(conference abstract)**

Reference	Study type/ methodological quality	Number of patients	Patient characteristics	Intervention	Comparison	Length follow-up	Outcome measures	Source funding
H Hasson, L Galli, G Gallotta, V Neri, P Blanc, M D'Annunzio, G Morsica, S Bagaglio, S Sollima, A Lazzarin, C Uberti Foppa. HAART simplification with lopinavir/ ritonavir monotherapy in HIV/HCV coinfected patients starting anti-HCV treatment: final results of a randomised, proof-of-principle clinical trial (KAMON 2 Study) IAS 2011: abstract no. CDB358 **(conference abstract)**	**RCT** **Allocation to treatment** Random Method of randomisation: unclear Concealment: unclear **Blinding** not blinded **Sample size calculation** not stated **ITT analysis** Yes **Setting:** Outpatients	**Total N: 30** 11 pts (36.6%) discontinued: 2 (1 in each arm, 6.7%) for toxicity (95%CI: -0.108+0.108). Among 9 withdrawn pts, 4 (36%) in A and 3 (27%) in B discontinued treatment for HCV virological failure; 2 (18%) were lost to follow-up.	**INCLUSION CRITERIA** HIV/HCV coinfected pts naïve for HCV treatment and requiring the start of anti-HCV therapy; stable HAART (>6 months); no previous virological failure or resistance to Protease Inhibitors; CD4+ >350cells/ mm^3 **EXCLUSION CRITERIA** Compensated cirrhosis **Baseline comparability between groups**: Baseline characteristic (age, gender, previous IDV use, HCV genotype, HIV duration, CD4 count, ALT) were not significantly different between A and B arms, except for Hb [13.9 (13.3-14.7) g/dL vs 15 (14.6-16.1) g/dL; p=0.017] **Age**: not stated **Gender**: not stated **Severity /Duration of disease**: not stated	**n=15** **Drug(s):** LPV/r monotherapy plus anti-HCV therapy (Peg-IFNα 2a + ribavirin (0.8-1.2 g/ die depending on body weight)	**n=15** **Drug(s):** LPV/r + Tenofovir/ emtricitabine plus anti-HCV therapy (Peg-IFNα 2a + ribavirin (0.8-1.2 g/ die depending on body weight)	**Treatment duration:** 48 weeks **Assessments at:** 48 and 72 weeks **Follow-up after end of treatment:** 24 weeks	**Primary endpoint:** the proportion of reduction or discontinuation of anti-HCV therapy through week 48. Other endpoints: virological response; CD4 count; blood counts and biochemistry	Not stated
Main outcomes: Sustained virological response was observed in 8/15 (53%) patients on monotherapy vs 10/15 pts (67%) under HAART. One transient HIV blip (RNA >50 copies/mL and ≤400 copies/mL) was observed in arm B.								

Other outcomes:

Bioparameter·¶ Serum· concentration¶ and·Units¤*	*Baseline¤*			*48·weeks¤*		*72·weeks¤*	
	A¤	**B¤**	*P·value¤*	**A¤**	**B¤**	**A¤**	**B¤**
				Immuno-virologic¤			
CD4·count·¶ x10³·Cells/mL¤	543·(402-663)¤	570·(451-842)¤	NS¤	267·(183-474)¤	321·(272-432)¤	556·(340-633)¤	456·(417-553)¤
HIV·RNA·copies/mL¤	49¤	49¤	NS¤	49¤	49¤	49¤	49¤
				Hepatic·toxicity¤			
ALT··U/L¤	66·(52-137)¤	85·(39-113)¤	NS¤	28·(18-40)¤	27·(24-52)¤	21·(19-44)¤	29·(16-63)¤
AST·U/L¤	42·(35-99)¤	42·(33-56)¤	NS¤	25·(22-33)¤	26·(23-36)¤	22·(19-30)¤	22·(16-30)¤
Lactic·acid·mM/L¤	1.0·(0.89-1.32)¤	1.5·(1.12-1.9)¤	P=0.045¤	1.14·(0.80-1.53)¤	1.37·(0.80-2.0)¤	1.43·(0.8-1.62)¤	1.45·(0.9-2.0)¤
Bilirubin,·total,·mg/dL¤	0.87·(0.68-1.03)¤	0.86·(0.7-1.11)¤	NS¤	0.51·(0.4-0.8)¤	0.59·(0.3-0.8)¤	0.6·(0.39-0.8)¤	0.6·(0.32-0.76)¤
Gamma-GT,·U/L¤	104·(46-152)¤	91·(46-174)¤	¤	39·(29-121)¤	37·(28-49)¤	39·(28-66)¤	27·(24-56)¤
Amylase·U/L¤	33·(30-40)¤	38·(34-62)¤	NS¤	29·(27-55)¤	45·(24-61)¤	31·(27-56)¤	38·(24-61)¤
Albumin·g/L¤	42·(39-45.4)¤	43.1·(41.3-46)¤	NS¤	41·(36.2-44.7)¤	42.2·(41-45.4)¤	43·(41.3-43.2)¤	44·(41-45)·¤
				Metabolic·toxicity¤			
Insulin·U/L¤	12·(6-17)¤	15.95-9.2-19)¤	NS¤	12.4·(7.17)¤	18.8·(10.6-26)¤	13.9·(7-17)¤	18.8·(10.6-26)¤
Glucose·mg/dL¤	80·(76-85)¤	88·(84-95)¤	NS¤	77·(72-83)¤	84·(77-88)¤	86·(79-88)¤	89·(84-93)¤
Cholesterol,·total· mg/dL¤	162·(153-196)¤	176·(160-205)¤	NS¤	174·(153-200)¤	175·(153-192)¤	186·(170-201)¤	190·(162-205)¤
HDL·Cholesterol· mg/dL¤	44·(29-49)¤	44·(40-50)¤	NS¤	35.5·(33-46)¤	39·(33-48)¤	36.5·(33-46)¤	39·(33-53)¤
LDL·Cholesterol· mg/dL¤	84·(69-101)¤	98·(82-120)¤	NS¤	79·(71-111)¤	88·(68-119)¤	86.5·(71-111)¤	109·(80-118)¤
Triglycerids·mg/dL¤	129·(97-149)¤	138·(105-199)¤	NS¤	189·(128-311)¤	157·(128-230)¤	221·(128-311)¤	156·(119-224)¤
Haemoglobin·mg/dL¤	14.3·(13.4-14.5)¤	15.3·(14-16)¤	P=0.017¤	11.3·(10.7-12.3)¤	12.4·(11.6-13.3)¤	12.7·(11.8-13.9)¤	14.6·(12.4-15.2)¤
White·Blood·Cells·¶ x103·Cells/mL¤	6·(4.8-7)¤	5.85·(5.1-7.34)¤	NS¤	2.7·(1.8-3.7)¤	3·(1.8-5)¤	4.5·(3.4-6)¤	5·(3.7-6.46)¤
Neutrophils·¶ x103·Cells/mL¤	3·(2.5-3.5)¤	2.79·(2.4-4.49)¤	NS¤	1.4·(1.0-1.7)¤	1.5·(0.9-2.8)¤	2.32·(1.6-3.0)¤	2.5·(1.9-5.01)¤
Platelets·x103·cells/mL·	214·(191-233)¤	206·(160-233)¤	NS¤	143·(116-177)¤	114·(100-186)¤	195·(147-224)¤	177·(125-223)¤

HCV virological efficacy was higher among 2/3 than 1/4 genotypes. Most biochemical parameters improved significantly during treatment in particular the hepatic AST and ALT ; Gamma-GT decreased more in arm B p=0.0185). Neutrophils increased more in arm B(p=0.0093). Blood glucose and total cholesterol slightly increased in each arm during the study, without exceeding normal values; conversely, triglycerides significantly increased in arm A.

Authors' conclusion

PI monotherapy + anti-HCV drugs was safe and effective as HAART + anti-HCV drugs

Atazanavir /r monotherapy

*Pulido F et al. Atazanavir/ritonavir monotherapy for maintenance of virologic suppression: 48 week primary analysis of the 96 week multicenter, open-label, single-arm, pilot OREY study. EACS
Year: 2009 *Abstract-No:* PS4/6 *Session:* PS4 - Antiretroviral Therapy I *Category:* 7.5 Treatment Simplification **(conference abstract)**

Further analysis of this publication showed that it should be excluded as it was not a randomised comparison of PI monotherapy versus continuation of combination therapy; all patients were switched to monotherapy.

Wilkin study: ClinicalTrials.gov identifier: NCT00084019

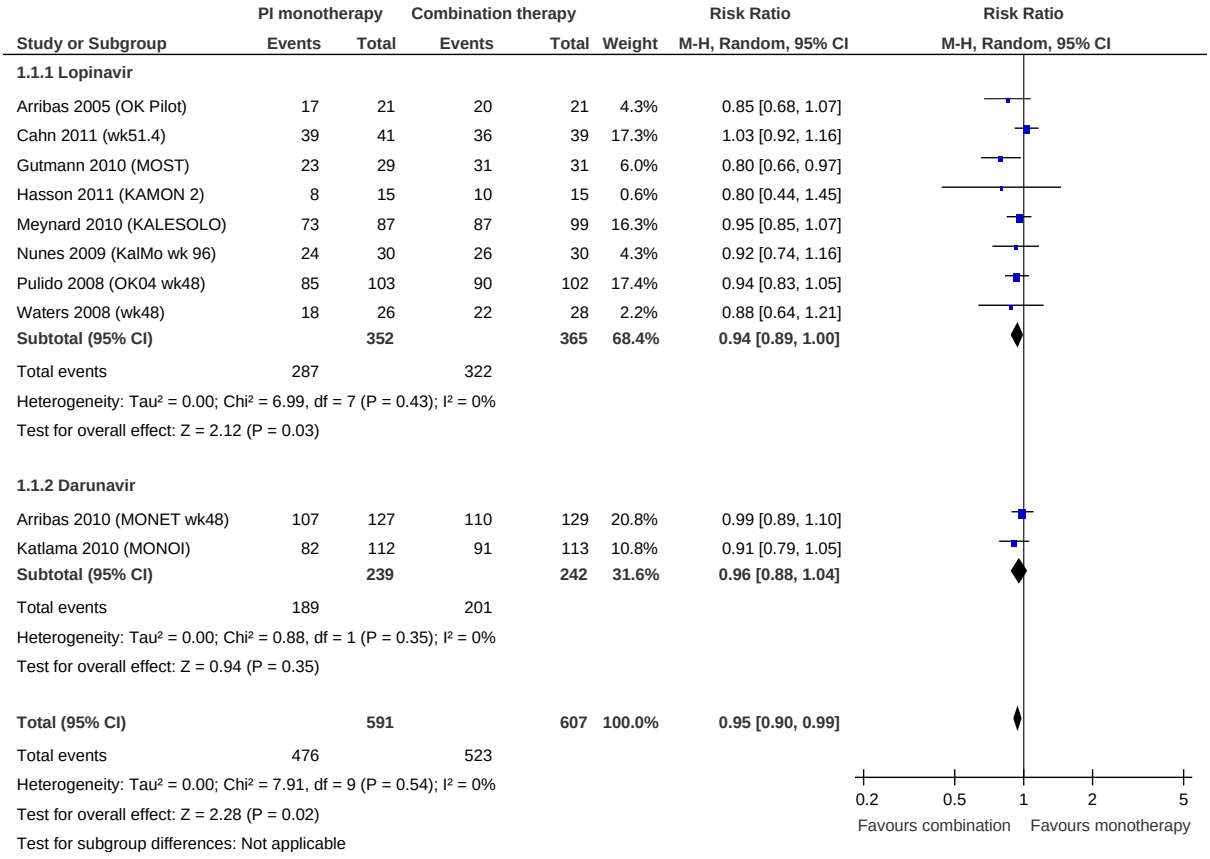
*Wilkin, T. J., J. E. McKinnon, et al. (2009). "Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy: final 48-week clinical and virologic outcomes." Journal of Infectious Diseases **199**(6): 866-871. ClinicalTrials.gov identifier: NCT00084019; AIDS Clinical Trials Group (ACTG) protocol 5201

This was a single-arm study - exclude

Waters study
Waters L, Jackson A, Singh K, Higgs C, Mandalia S, et al. (2008) The impact of continued HAART versus lopinavir/ritonavir monotherapy (mLPV/r) on body fat and bone mineral density (BMD) as measured by DEXA: 48 week results of a randomised study. XVII International AIDS Conference, August 3-8, 2008, Mexico City, Mexico Abstract CDB0193.(P88).

Reference	Study type/ methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Length follow-up	Outcome measures	Source funding
Waters L, Jackson A, Singh K, Higgs C, Mandalia S, et al. (2008) The impact of continued HAART versus lopinavir/ritonavir monotherapy (mLPV/r) on body fat and bone mineral density (BMD) as measured by DEXA: 48 week results of a randomised study. XVII International AIDS Conference, August 3-8, 2008, Mexico City, Mexico Abstract CDB0193.(P88). **(conference abstract)**	**RCT** **Allocation to treatment** Random/ Method of randomisation: unclear Concealment: unclear **Blinding** not blinded **Sample size calculation** not stated **ITT analysis** Yes **Setting:** Outpatients	**Total N: 54**	**INCLUSION CRITERIA** Subjects on suppressive HAART (2 NRTI and NNRTI or PI/r) with <5 PI mutations **EXCLUSION CRITERIA:** not stated **Baseline comparability between groups**: yes **Age**: not stated **Gender**: not stated **Severity /Duration of disease**: not stated	**n=26** **Drug(s):** lopinavir/ ritonavir monotherapy	**n=28** **Drug(s):** continue HAART	**Treatment duration:** 48 weeks **Assessments at:** not stated **Follow-up after end of treatment:** none	**Primary endpoint:** viral load, CD4, safety parameters, QoL, DEXA scans	Not stated
Main outcomes: Viral load <50 at 48 weeks: 18/26 monotherapy and 22/28 HAART. Other outcomes: Change in DEXA not significant for either arm. Small median increase in limb fat on monotherapy (13.3% vs. 7% on HAART, p=0.92) and an increase of 15.3% in trunk fat on monotherapy vs. 0.5% on HAART (p=0.05). **Authors' conclusion** Switch to monotherapy is associated with maintained viral suppression and greater increase in trunk fat than HAART. Limb fat and BMD were similar and stable at 48 weeks.								

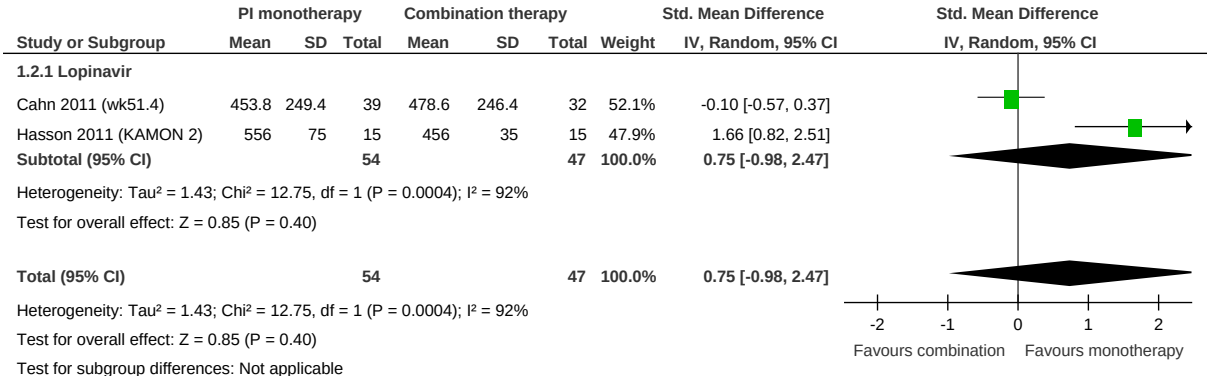
Forest plots for comparisons of PI monotherapy versus combination therapy.
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.1 Virological suppression.



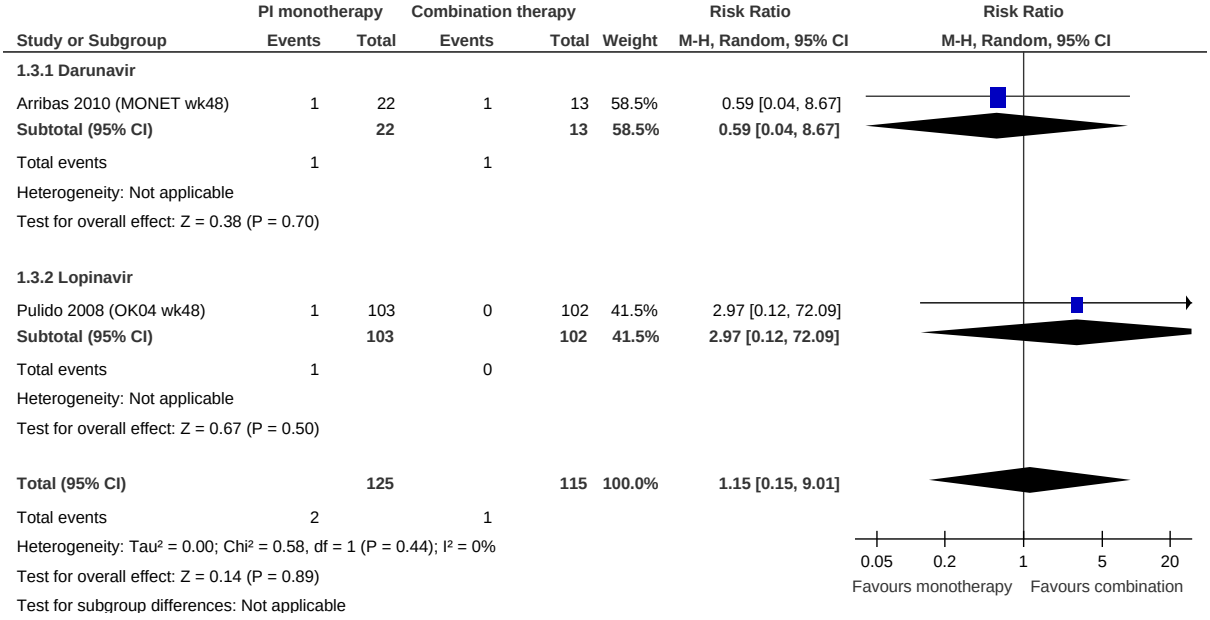
Combination therapy was superior to monotherapy for virological suppression.

There were no significant differences between the groups for the outcomes of CD4 count; drug resistance; serious adverse events; grade 3 nervous system or psychiatric adverse events; Grade 3 raised LFTs; Grade 3-4 abnormalities in lipase; Grade 3 abnormalities in total cholesterol; Grade 3-4 abnormalities in low-density lipoprotein; Grade 3-4 abnormalities in triglycerides; Grade 3-4 abnormalities in haemoglobin; Grade 3-4 abnormalities in neutrophils; Grade 3 or 4 infectious disease events; Grade 3 or 4 cardiovascular disease events; Lipodystrophy (any grade) or CNS disease (including Functional Assessment of HIV infection).

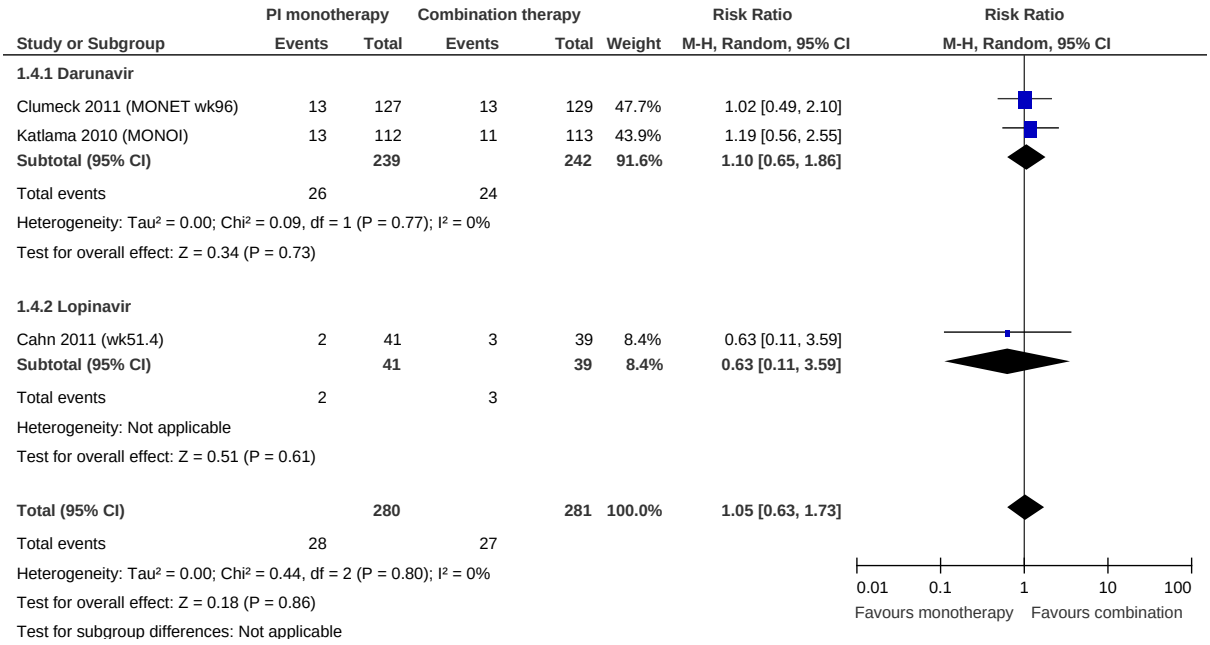
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.2 CD4 count.



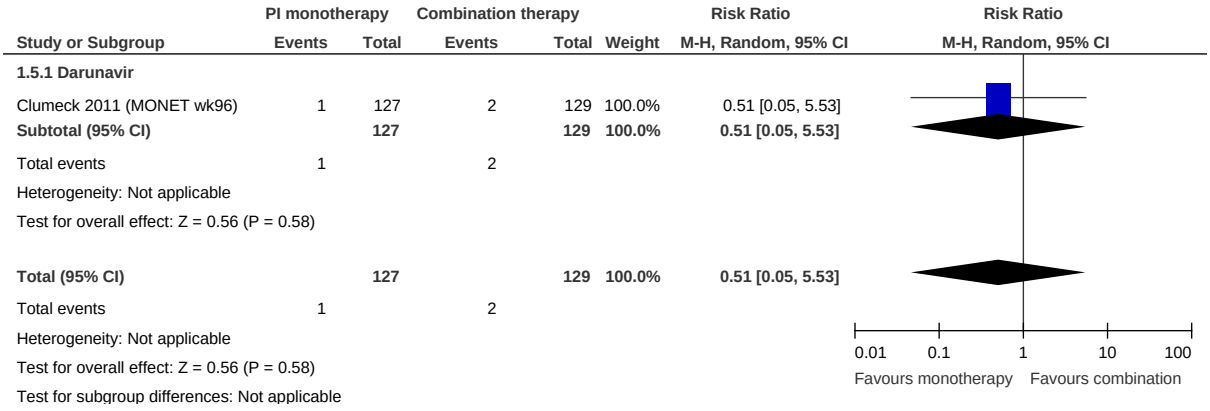
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.3 Drug resistance.



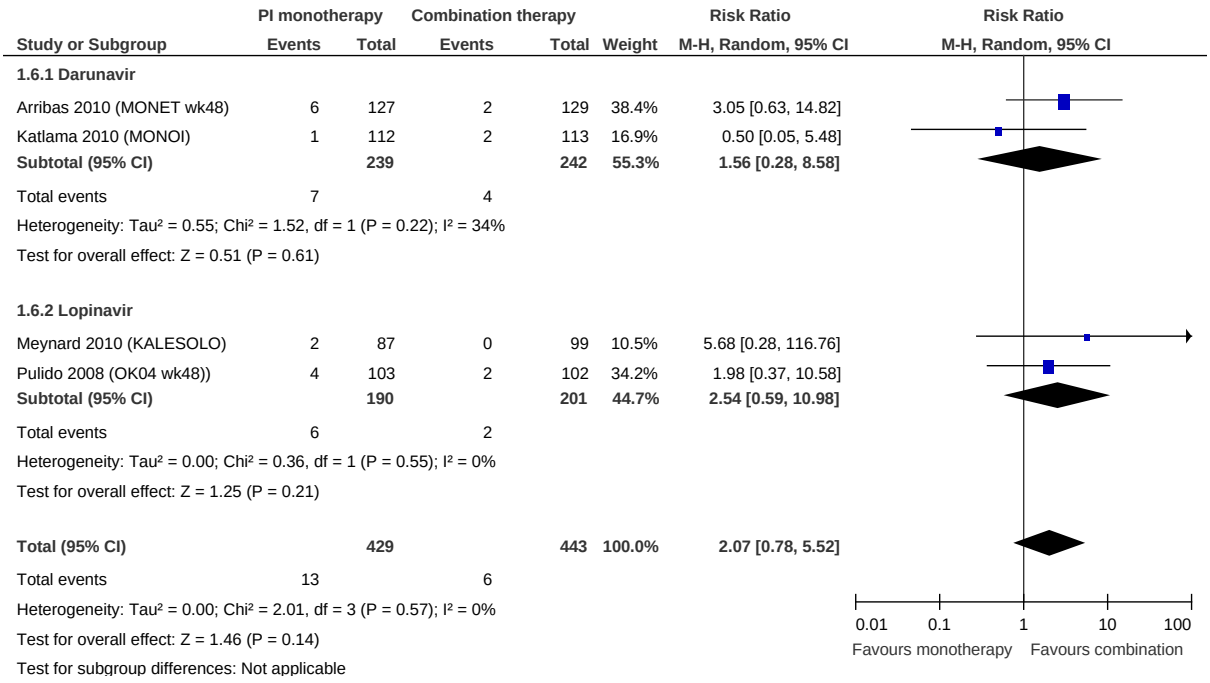
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.4 Serious adverse events.



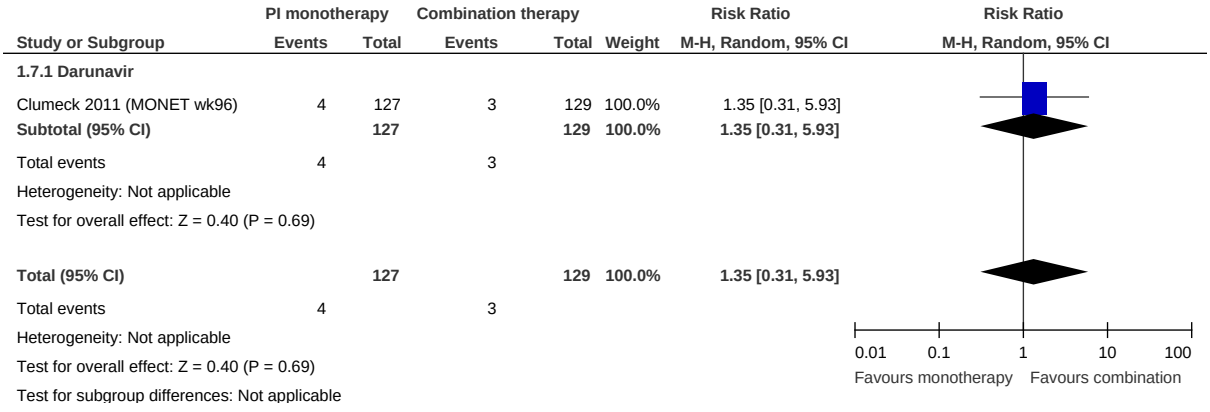
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.5 Grade 3 nervous system or psychiatric adverse event.



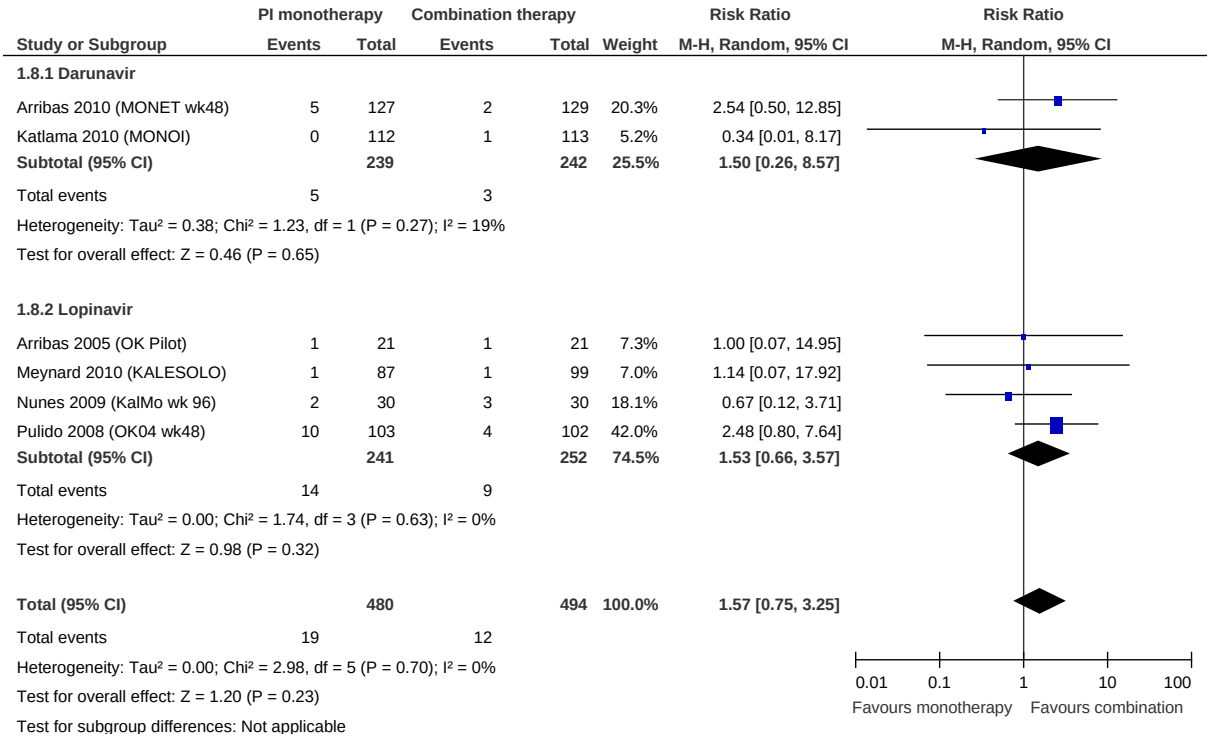
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.6 Grade 3 raised LFTs.



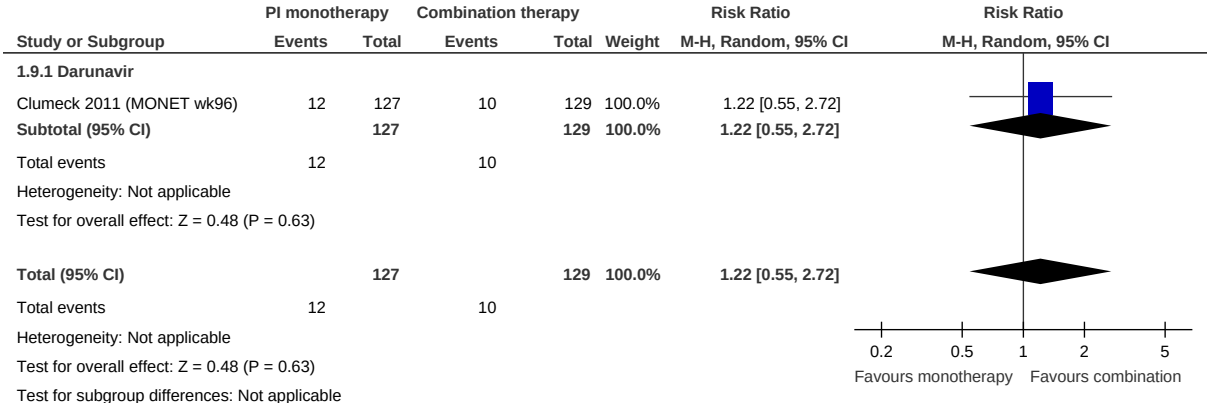
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.7 Grade 3-4 abnormalities in lipase.



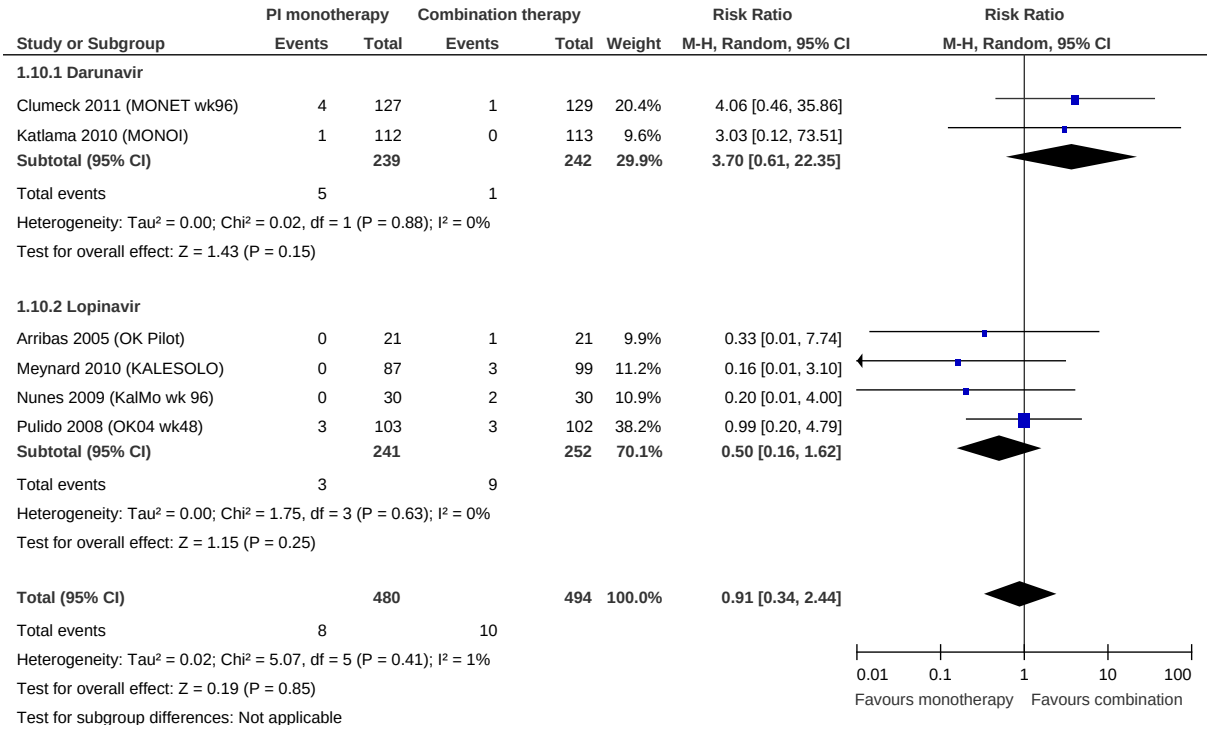
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.8 Grade 3 abnormalities in total cholesterol.



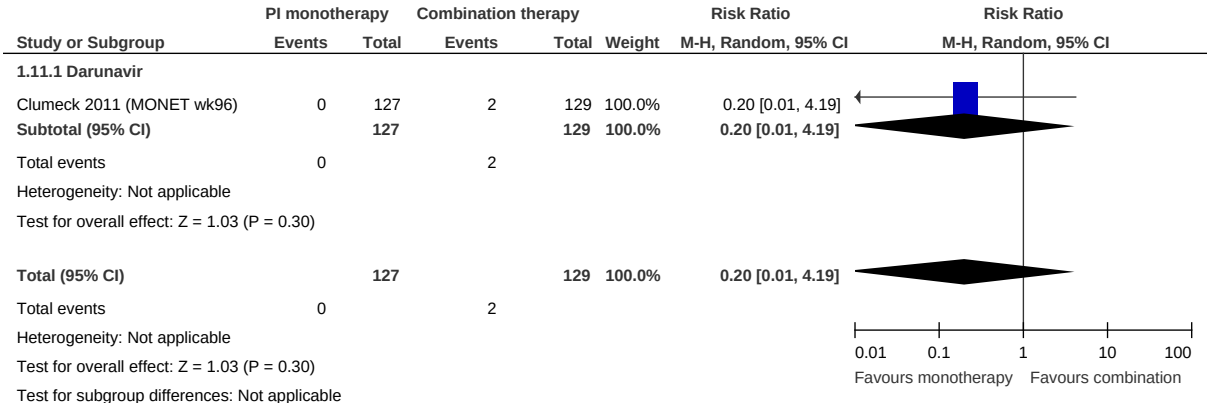
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.9 Grade 3-4 abnormalities in low-density lipoprotein.



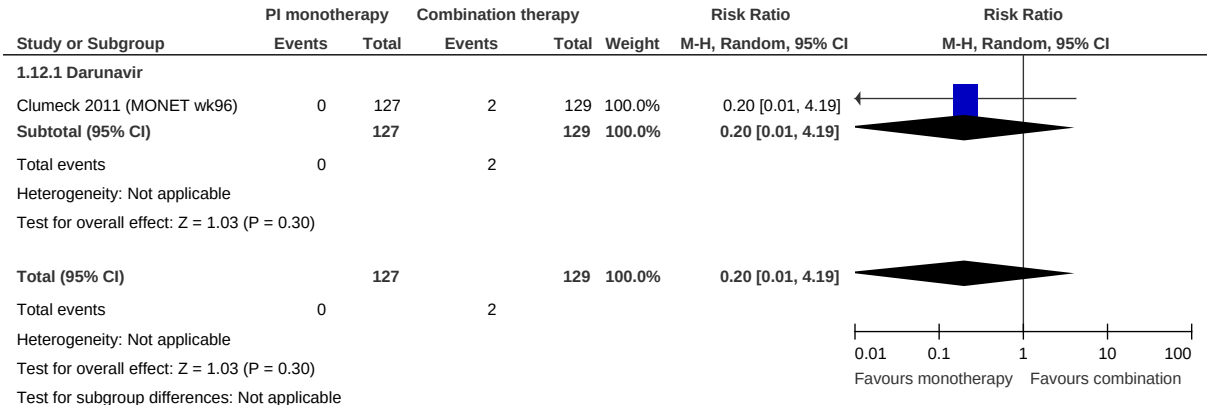
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.10 Grade 3-4 abnormalities in triglycerides.



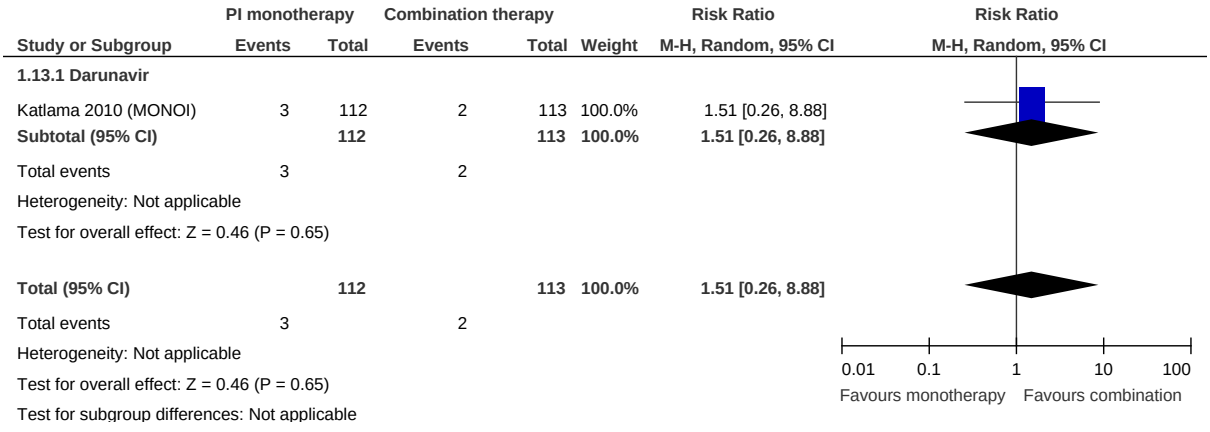
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.11 Grade 3-4 abnormalities in haemoglobin.



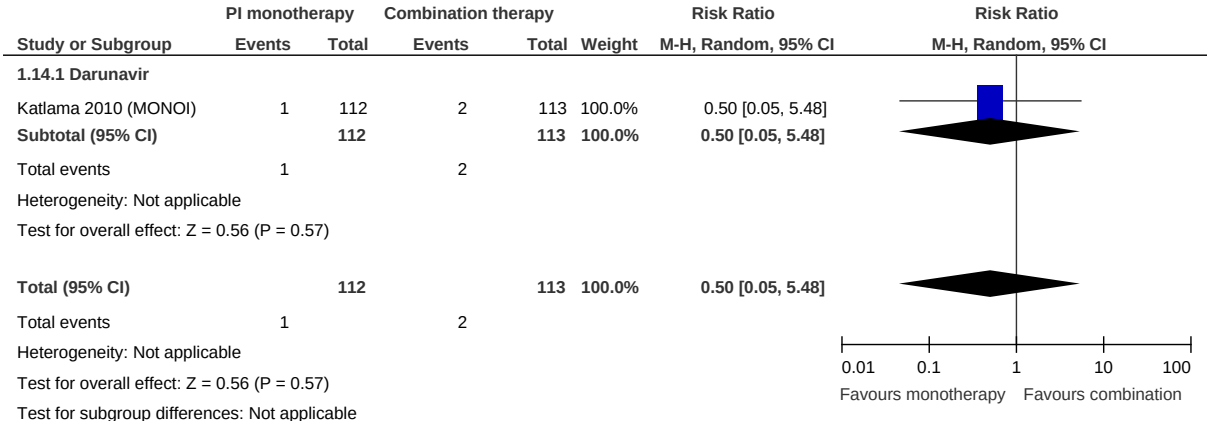
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.12 Grade 3-4 abnormalities in neutrophils.



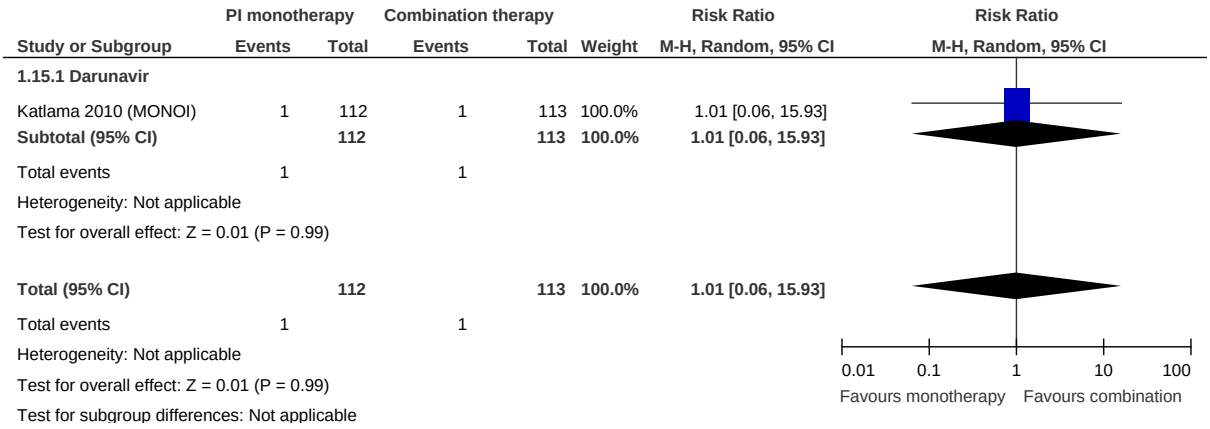
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.13 Grade 3 or 4 infectious disease events.



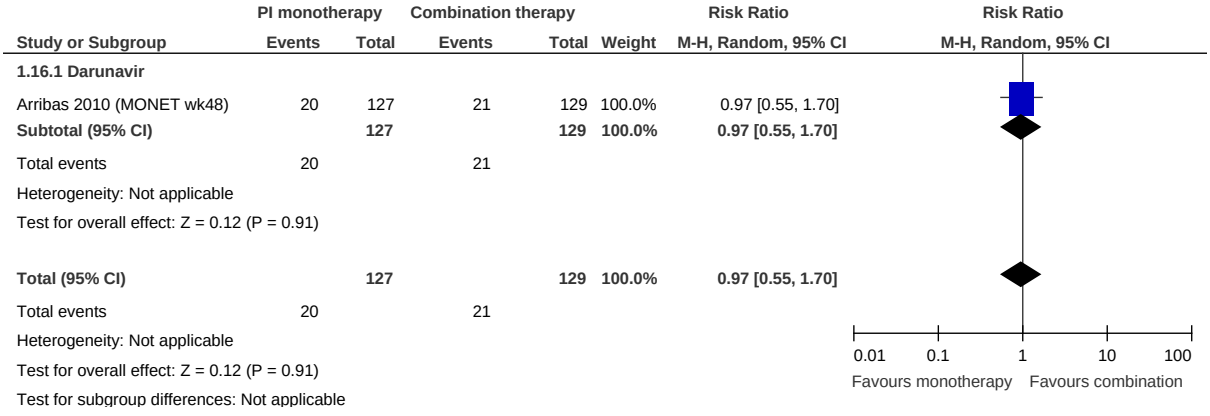
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.14 Grade 3 or 4 cardiovascular disease events.



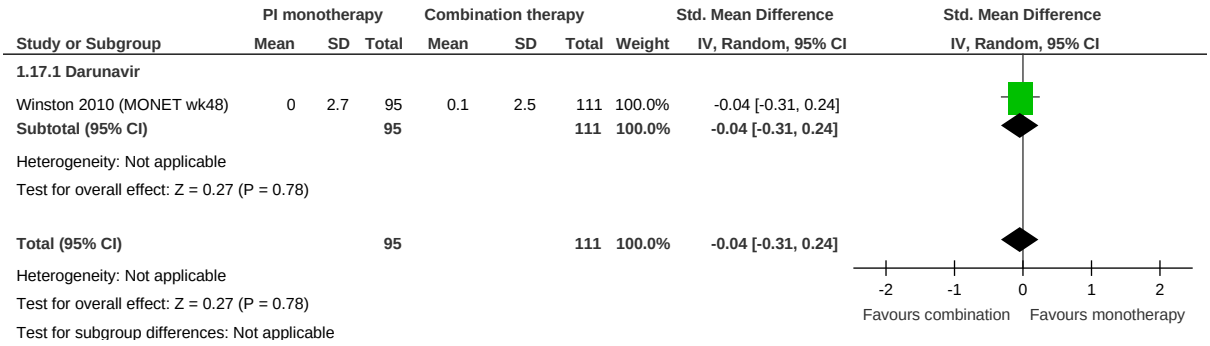
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.15 Lipodystrophy (any grade).



Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.16 CNS disease (any grade).



Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.17 Functional Assessment of HIV infection.



GRADE table for PI monotherapy versus combination therapy for HIV

The outcomes have been classified as follows:

Viral suppression: Critical for decision-making (9/9); CD4 count: Critical for decision-making (8/9); Drug resistance: Critical for decision-making (7/9); Serious adverse events: Important for decision-making (6/9); any grade 3-4 adverse event outcomes: Important for decision-making (5/9); lipodystrophy (any grade) or CNS disease (any grade): Important for decision-making (4/9); change in Functional Assessment of HIV infection: not important for decision-making (3/9).

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PI monotherapy versus combination therapy	control	Relative (95% CI)	Absolute		
Virological suppresion (follow-up 48-96 weeks; viral load <50)												
10	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	476/591 (80.5%)	523/607 (86.2%)	RR 0.95 (0.9 to 0.99)	43 fewer per 1000 (from 9 fewer to 86 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								87.3%		44 fewer per 1000 (from 9 fewer to 87 fewer)		
Virological suppresion - Lopinavir (follow-up 48-96 weeks; viral load < 50)												
8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	287/352 (81.5%)	322/365 (88.2%)	RR 0.94 (0.89 to 1)	53 fewer per 1000 (from 97 fewer to 0 more)	⊕⊕⊕O MODERATE	CRITICAL
								88.1%		53 fewer per 1000 (from 97 fewer to 0 more)		
Virological suppresion - Darunavir (follow-up 48 weeks; viral load <50)												

2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	189/239 (79.1%)	201/242 (83.1%) 82.9%	RR 0.96 (0.88 to 1.04)	33 fewer per 1000 (from 100 fewer to 33 more) 33 fewer per 1000 (from 99 fewer to 33 more)	⊕⊕⊕O MODERATE	CRITICAL
CD4 count (follow-up 48-51.4 weeks; measured with: CD4 cell count; Better indicated by higher values)												
2	randomised trials	serious[1]	very serious[2]	no serious indirectness	serious[3]	none	54	47	-	SMD 0.75 higher (0.98 lower to 2.47 higher)	⊕OOO VERY LOW	CRITICAL
CD4 count - Lopinavir (follow-up 48-51.4 weeks; measured with: CD4 cell count; Better indicated by higher values)												
2	randomised trials	serious[1]	very serious[2]	no serious indirectness	serious[3]	none	54	47	-	SMD 0.75 higher (0.98 lower to 2.47 higher)	⊕OOO VERY LOW	CRITICAL
Drug resistance (follow-up 48 weeks; genotypic testing)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/125 (1.6%)	1/115 (0.9%) 3.9%	RR 1.15 (0.15 to 9.01)	1 more per 1000 (from 7 fewer to 70 more) 6 more per 1000 (from 33 fewer to 312 more)	⊕OOO VERY LOW	CRITICAL
Drug resistance - Darunavir (follow-up 48 weeks; genotypic testing)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/22 (4.5%)	1/13 (7.7%) 7.7%	RR 0.59 (0.04 to 8.67)	32 fewer per 1000 (from 74 fewer to 590 more) 32 fewer per 1000 (from 74 fewer to 591 more)	⊕OOO VERY LOW	CRITICAL
Drug resistance - Lopinavir (follow-up 48 weeks; genotypic testing)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[4]	none	1/103 (1%)	0/102 (0%)	RR 2.97 (0.12 to 72.09)	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕OO	CRITICAL

								0%		0 more per 1000 (from 0 fewer to 0 more)	LOW	
Serious adverse events (follow-up 48-96 weeks; monitoring)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	28/280 (10%)	27/281 (9.6%)	RR 1.05 (0.63 to 1.73)	5 more per 1000 (from 36 fewer to 70 more)	⊕⊕⊕O MODERATE	IMPORTANT
								9.7%		5 more per 1000 (from 36 fewer to 71 more)		
Serious adverse events - Darunavir (follow-up 48-96 weeks; monitoring)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/239 (10.9%)	24/242 (9.9%)	RR 1.1 (0.65 to 1.86)	10 more per 1000 (from 35 fewer to 85 more)	⊕⊕⊕O MODERATE	IMPORTANT
								9.9%		10 more per 1000 (from 35 fewer to 85 more)		
Serious adverse events - Lopinavir (follow-up 51.4 weeks; monitoring)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[4]	none	2/41 (4.9%)	3/39 (7.7%)	RR 0.63 (0.11 to 3.59)	28 fewer per 1000 (from 68 fewer to 199 more)	⊕⊕OO LOW	IMPORTANT
								7.7%		28 fewer per 1000 (from 69 fewer to 199 more)		
Grade 3 nervous system or psychiatric adverse event (follow-up 96 weeks; monitoring)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/127 (0.8%)	2/129 (1.6%)	RR 0.51 (0.05 to 5.53)	8 fewer per 1000 (from 15 fewer to 70 more)	⊕OOO VERY LOW	IMPORTANT
								1.6%		8 fewer per 1000 (from 15 fewer to 72 more)		
Grade 3 nervous system or psychiatric adverse event - Darunavir (follow-up 96 weeks; monitoring)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/127 (0.8%)	2/129 (1.6%)	RR 0.51 (0.05 to 5.53)	8 fewer per 1000 (from 15 fewer to 70 more)	⊕OOO VERY LOW	IMPORTANT
								1.6%		8 fewer per 1000 (from		

										15 fewer to 72 more)		
Grade 3 raised LFTs (follow-up 48 weeks; monitoring)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	13/429 (3%)	6/443 (1.4%) 1.7%	RR 2.07 (0.78 to 5.52)	14 more per 1000 (from 3 fewer to 61 more) 18 more per 1000 (from 4 fewer to 77 more)	⊕OOO VERY LOW	IMPORTANT
Grade 3 raised LFTs - Darunavir (follow-up 48 weeks; monitoring)												
2	randomised trials	serious[1]	serious[5]	no serious indirectness	very serious[4]	none	7/239 (2.9%)	4/242 (1.7%) 1.7%	RR 1.56 (0.28 to 8.58)	9 more per 1000 (from 12 fewer to 125 more) 10 more per 1000 (from 12 fewer to 129 more)	⊕OOO VERY LOW	IMPORTANT
Grade 3 raised LFTs - Lopinavir (follow-up 48 weeks; monitoring)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[4]	none	6/190 (3.2%)	2/201 (1%) 1%	RR 2.54 (0.59 to 10.98)	15 more per 1000 (from 4 fewer to 99 more) 15 more per 1000 (from 4 fewer to 100 more)	⊕⊕OO LOW	IMPORTANT
Grade 3-4 abnormalities in lipase (follow-up 96 weeks; monitoring)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	4/127 (3.1%)	3/129 (2.3%) 2.3%	RR 1.35 (0.31 to 5.93)	8 more per 1000 (from 16 fewer to 115 more) 8 more per 1000 (from 16 fewer to 113 more)	⊕OOO VERY LOW	IMPORTANT
Grade 3-4 abnormalities in lipase - Darunavir												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	4/127 (3.1%)	3/129 (2.3%) 2.3%	RR 1.35 (0.31 to 5.93)	8 more per 1000 (from 16 fewer to 115 more) 8 more per 1000 (from 16 fewer to 113 more)	⊕OOO VERY LOW	IMPORTANT
Grade 3 abnormalities in total cholesterol (follow-up 48-96 weeks; monitoring)												

6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	19/480 (4%)	12/494 (2.4%) 2.7%	RR 1.57 (0.75 to 3.25)	14 more per 1000 (from 6 fewer to 55 more) 15 more per 1000 (from 7 fewer to 61 more)	⊕⊕OO LOW	IMPORTANT
Grade 3 abnormalities in total cholesterol - Darunavir (follow-up 48 weeks; monitoring)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/239 (2.1%)	3/242 (1.2%) 1.2%	RR 1.5 (0.26 to 8.57)	6 more per 1000 (from 9 fewer to 94 more) 6 more per 1000 (from 9 fewer to 91 more)	⊕OOO VERY LOW	IMPORTANT
Grade 3 abnormalities in total cholesterol - Lopinavir (follow-up 48-96 weeks; monitoring)												
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[4]	none	14/241 (5.8%)	9/252 (3.6%) 4.3%	RR 1.53 (0.66 to 3.57)	19 more per 1000 (from 12 fewer to 92 more) 23 more per 1000 (from 15 fewer to 111 more)	⊕⊕OO LOW	IMPORTANT
Grade 3-4 abnormalities in low-density lipoprotein (follow-up 96 weeks; monitoring)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	12/127 (9.4%)	10/129 (7.8%) 7.8%	RR 1.22 (0.55 to 2.72)	17 more per 1000 (from 35 fewer to 133 more) 17 more per 1000 (from 35 fewer to 134 more)	⊕⊕OO LOW	IMPORTANT
Grade 3-4 abnormalities in low-density lipoprotein - Darunavir (follow-up 96 weeks; monitoring)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	12/127 (9.4%)	10/129 (7.8%) 7.8%	RR 1.22 (0.55 to 2.72)	17 more per 1000 (from 35 fewer to 133 more) 17 more per 1000 (from 35 fewer to 134 more)	⊕⊕OO LOW	IMPORTANT
Grade 3-4 abnormalities in triglycerides (follow-up 48-96 weeks; monitoring)												
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	8/480 (1.7%)	10/494 (2%)	RR 0.91 (0.34 to 2.44)	2 fewer per 1000 (from 13 fewer to 29 more)	⊕OOO	IMPORTANT

								3%		3 fewer per 1000 (from 20 fewer to 43 more)	VERY LOW	
Grade 3-4 abnormalities in triglycerides - Darunavir (follow-up 48-96 weeks; monitoring)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/239 (2.1%)	1/242 (0.4%)	RR 3.7 (0.61 to 22.35)	11 more per 1000 (from 2 fewer to 88 more)	⊕OOO VERY LOW	IMPORTANT
								0.4%		11 more per 1000 (from 2 fewer to 85 more)		
Grade 3-4 abnormalities in triglycerides - Lopinavir (follow-up 48-96 weeks; monitoring)												
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[4]	none	3/241 (1.2%)	9/252 (3.6%)	RR 0.5 (0.16 to 1.62)	18 fewer per 1000 (from 30 fewer to 22 more)	⊕⊕OO LOW	IMPORTANT
								3.9%		20 fewer per 1000 (from 33 fewer to 24 more)		
Grade 3-4 abnormalities in haemoglobin (follow-up 96 weeks; monitoring)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/127 (0%)	2/129 (1.6%)	RR 0.2 (0.01 to 4.19)	12 fewer per 1000 (from 15 fewer to 49 more)	⊕OOO VERY LOW	IMPORTANT
								1.6%		13 fewer per 1000 (from 16 fewer to 51 more)		
Grade 3-4 abnormalities in haemoglobin - Darunavir (follow-up 96 weeks; monitoring)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/127 (0%)	2/129 (1.6%)	RR 0.2 (0.01 to 4.19)	12 fewer per 1000 (from 15 fewer to 49 more)	⊕OOO VERY LOW	IMPORTANT
								1.6%		13 fewer per 1000 (from 16 fewer to 51 more)		
Grade 3-4 abnormalities in neutrophils (follow-up 96 weeks; monitoring)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/127 (0%)	2/129 (1.6%) 1.6%	RR 0.2 (0.01 to 4.19)	12 fewer per 1000 (from 15 fewer to 49 more) 13 fewer per 1000 (from 16 fewer to 51 more)	⊕OOO VERY LOW	IMPORTANT
Grade 3-4 abnormalities in neutrophils - Darunavir (follow-up 96 weeks; monitoring)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/127 (0%)	2/129 (1.6%) 1.6%	RR 0.2 (0.01 to 4.19)	12 fewer per 1000 (from 15 fewer to 49 more) 13 fewer per 1000 (from 16 fewer to 51 more)	⊕OOO VERY LOW	IMPORTANT
Grade 3 or 4 infectious disease events (follow-up 48 weeks; monitoring)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	3/112 (2.7%)	2/113 (1.8%) 1.8%	RR 1.51 (0.26 to 8.88)	9 more per 1000 (from 13 fewer to 139 more) 9 more per 1000 (from 13 fewer to 142 more)	⊕OOO VERY LOW	IMPORTANT
Grade 3 or 4 infectious disease events - Darunavir (follow-up 48 weeks; monitoring)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	3/112 (2.7%)	2/113 (1.8%) 1.8%	RR 1.51 (0.26 to 8.88)	9 more per 1000 (from 13 fewer to 139 more) 9 more per 1000 (from 13 fewer to 142 more)	⊕OOO VERY LOW	IMPORTANT
Grade 3 or 4 cardiovascular disease events (follow-up 48 weeks; monitoring)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/112 (0.9%)	2/113 (1.8%) 1.8%	RR 0.5 (0.05 to 5.48)	9 fewer per 1000 (from 17 fewer to 79 more) 9 fewer per 1000 (from 17 fewer to 81 more)	⊕OOO VERY LOW	IMPORTANT

Grade 3 or 4 cardiovascular disease events - Darunavir (follow-up 48 weeks; monitoring)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/112 (0.9%)	2/113 (1.8%)	RR 0.5 (0.05 to 5.48)	9 fewer per 1000 (from 17 fewer to 79 more)	⊕OOO VERY LOW	IMPORTANT
								1.8%		9 fewer per 1000 (from 17 fewer to 81 more)		
Lipodystrophy (any grade) (follow-up 48 weeks; monitoring)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/112 (0.9%)	1/113 (0.9%)	RR 1.01 (0.06 to 15.93)	0 more per 1000 (from 8 fewer to 132 more)	⊕OOO VERY LOW	IMPORTANT
								0.9%		0 more per 1000 (from 8 fewer to 134 more)		
Lipodystrophy (any grade) - Darunavir (follow-up 48 weeks; monitoring)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/112 (0.9%)	1/113 (0.9%)	RR 1.01 (0.06 to 15.93)	0 more per 1000 (from 8 fewer to 132 more)	⊕OOO VERY LOW	IMPORTANT
								0.9%		0 more per 1000 (from 8 fewer to 134 more)		
CNS disease (follow-up 48 weeks; monitoring)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/127 (15.7%)	21/129 (16.3%)	RR 0.97 (0.55 to 1.7)	5 fewer per 1000 (from 73 fewer to 114 more)	⊕⊕⊕O MODERATE	IMPORTANT
								16.3%		5 fewer per 1000 (from 73 fewer to 114 more)		
CNS disease - Darunavir (follow-up 48 weeks; monitoring)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/127 (15.7%)	21/129 (16.3%)	RR 0.97 (0.55 to 1.7)	5 fewer per 1000 (from 73 fewer to 114 more)	⊕⊕⊕O MODERATE	IMPORTANT
								16.3%		5 fewer per 1000 (from 73 fewer to 114 more)		
Functional Assessment of HIV infection (follow-up 48 weeks; measured with: Change in Functional Assessment of HIV Infection score; Better indicated by higher values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	95	111	-	SMD 0.04 lower (0.31 lower to 0.24 higher)	⊕⊕⊕O MODERATE	NOT IMPORTANT
Functional Assessment of HIV infection - Darunavir (follow-up 48 weeks; measured with: Change in Functional Assessment of HIV Infection; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	95	111	-	SMD 0.04 lower (0.31 lower to 0.24 higher)	⊕⊕⊕O MODERATE	NOT IMPORTANT

[1] randomisation and allocation concealment unclear in some studies
[2] I2 > 80% indicates inconsistency between studies
[3] Wide confidence intervals indicates imprecision
[4] Very small numbers of events
[5] I2 between 20 and 50% indicates some inconsistency