Appendix 3: Grade tables

3.2. What to Start: Which third agent

Design: RCTs, Systematic reviews
Population: ART naive
Intervention: which third agent (Efavirenz, Raltegravir, Darunavir/ritonavir, Atazanavir/ritonavir)
Outcomes: Viral load, CD4 count, HIV resistance, adverse events, clinical events

The table below outlines key outcomes and an importance rating (based on GRADE) for each.

OUTCOME	IMPORTANCE
Viral suppression (<50) at week 48	9: critical
Viral suppression at week 96	8: critical
Proportion of all randomised subjects with protocol-defined virological failure at week 48 +/- week 96	9: critical
Proportion of all randomised subjects who develop drug resistance	8: critical
Proportion discontinuing for adverse events	7: critical
Proportion with grade 3/4 adverse events (overall)	7: critical
Proportion with grade 3/4 adverse events (clinical)	7: critical
Proportion with grade 3/4 adverse events (laboratory)	6: important
Proportion with grade 3/4 CNS events	5: important
Proportion with grade 3/4 diarrhoea	5: important
Proportion with grade 3/4 ALT/AST elevation	7: critical
Proportion with grade 3/4 total cholesterol events	3: not important
Proportion with grade 3/4 LDL cholesterol	3: not important
Proportion with grade 3/4 triglycerides	3: not important
Renal impairment	4: important
Total hip BMD decrease 6% or more	3: not important
Total spine BMD decrease 6% or more	3: not important
Change in lumbar spine BMD	3: not important
Change in hip BMD	3: not important
Bone fractures	3: not important

10% or more limb fat loss	5: important
% change in limb fat	5: important
% change in trunk fat	5: important
% change in visceral adipose tissue	5: important
Change in visceral:total adipose tissue ratio	5: important

A **Atazanavir/r versus Efavirenz**

Two randomised trials were found comparing etavirenz versus atazanavir:

- ALTAIR study:
  - Puls, R. L., P. Srasuebkul, et al. (2010). "Efavirenz versus boosted atazanavir or zidovudine and abacavir in antiretroviral treatment-naive, HIV-infected subjects: week 48 data from the Altair study." Clinical Infectious Diseases 51(7): 855-864.
  - Winston A et al. Does Choice of Combination Antiretroviral Therapy (cART) Alter Changes in Cerebral Function Testing after 48 Weeks in Treatment-Naive, HIV-1–Infected Individuals Commencing cART? A Randomized, Controlled Study. Clinical Infectious Diseases 2010; 50:920–929
- ACTG5202:
  - Sax *et al.* Abacavir–Lamivudine versus Tenofovir–Emtricitabine for Initial HIV-1 Therapy. New Engl J Med 2009; 361(23): 2230-40 (ClinicalTrials.gov number, NCT00118898).
  - Sax *et al.* Abacavir/ Lamivudine Versus Tenofovir DF/Emtricitabine as Part of Combination Regimens for Initial Treatment of HIV: Final Results. J Infect Dis 2011; 204: 1191–201.
  - Daar ES et al. Atazanavir Plus Ritonavir or Efavirenz as Part of a 3-Drug Regimen for Initial Treatment of HIV-1 A Randomized Trial. *Ann Intern Med.* 2011;154:445-456.
  - McComsey GA *et al*. Bone Mineral Density and Fractures in Antiretroviral-Naive Persons Randomized to Receive Abacavir-Lamivudine or Tenofovir Disoproxil Fumarate-Emtricitabine Along With Efavirenz or Atazanavir-Ritonavir: AIDS Clinical Trials Group A5224s, a Substudy of ACTG A5202. J Infect Dis 2011; 203: 1791-801.
  - McComsey GA *et al*. Peripheral and Central Fat Changes in Subjects Randomized to Abacavir-Lamivudine or Tenofovir-Emtricitabine With Atazanavir-Ritonavir or Efavirenz: ACTG Study A5224s. Clinical Infectious Diseases 2011;53(2):185–196.

Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
Puls, R. L., P. Srasuebkul, et al. (2010). "Efavirenz versus boosted atazanavir or zidovudine and abacavir in antiretroviral treatment-naive, HIV-infected subjects: week 48 data from the Altair study." Clinical Infectious Diseases 51(7): 855-864. Winston A et al. Does Choice of Combination Antiretroviral Therapy	**RCT** **Allocation to treatment** Random Method of randomisation: Randomization was stratified for clinical site and plasma HIV-RNA <100,000 or ≥100,000 copies/mL at baseline. Concealment: unclear **Blinding** not blinded **Sample size calculation** yes **ITT analysis** Yes **Setting:** Outpatients	**Total N: 329** Winston substudy n=30 (9, 9, and 12 subjects in arms 1, 2, and 3, respectively)	**INCLUSION CRITERIA** healthy, ART-naive, adult HIV-infected pts with CD4+ cell counts 150 cells/mL and plasma HIV-1 RNA 12000 copies/mL. Pts were required to have laboratory parameters within protocol specified ranges, creatinine clearance of ≥70 mL/min (Cockcroft-Gault), and no evidence of HIV-drug resistance **EXCLUSION CRITERIA** HLA-B*5701–positive, were pregnant and/or breast-feeding, used prohibited substances, had serious infection or illness requiring intervention, or had known renal insufficiency, obstructive liver disease, intractable diarrhoea, cardiomyopathy, or substantial cardiovascular disease **Baseline comparability between groups**: yes **Age**: mean 36.6 SD 9.2 years **Gender**: 76% male **Severity of disease:** mean CD4	**Drug(s):** 600 mg once daily EFV (Arm I) combined with TDF-FTC (fixed dose combination, i.e. Truvada) **Arm I n=114**	**Drug(s):** r/ATV (Arm II) or 250 mg or 300 mg twice daily ZDV plus 600 mg once daily ABC (Arm III), combined with TDF-FTC (fixed dose combination, i.e. Truvada) **Arm II n=105; Arm III n=103**	**Treatment duration:** 96 weeks **Assessments at:** weeks 0, 4, 12, 24, 36, and 48 **Follow-up after end of treatment:** none	**Primary endpoint:** time-weighted area under the curve (TWAUC) mean change from baseline plasma HIV-RNA to wk 48 by treatment arm. Proportions of pts with plasma HIV-RNA <50 copies/mL, <200 copies/mL (principal measure), and <400 copies/mL. 200 copies/mL) Other endpoints: physical examination, adverse events, clinical biochemistry, haematology, T cell subsets, quality of life (SF-12 questionnaire); assessment of stress, anxiety, and depression (DASS-21 questionnaire); and timed gait tests; 10-year Framingham risk Winston substudy: changes in cerebral function testing:	The Australian Government Department of Health and Ageing; Gilead Sciences

(cART) Alter Changes in Cerebral Function Testing after 48 Weeks in Treatment-Naive, HIV–Infected Individuals Commencing cART? A Randomized, Controlled Study. Clinical Infectious Diseases 2010; 50:920–929			cell count 229 SD 115 cells/ml Winston substudy: Specific exclusion criteria were: current or recent use of antidepressant or antipsychotic therapies, current or recent history of alcohol or recreational drug dependence, recent significant head injury, established dementia, active opportunistic infections, untreated early syphilis, hepatitis C infection (i.e. positive for hepatitis C antibody), and/or evidence of established chronic liver disease, cirrhosis, or hepatic encephalopathy (in the previous 12 weeks); in the 48-h period prior to study investigations being performed, consumption of alcohol or caffeine was not permitted.				neurocognitive function testing at baseline and week 48 (***Cognitive testing:*** A computerized cognitive test battery [CogState] that has been validated for HIV-1–infected subjects; domains were detection, identification, learning [matching learning and associate learning], monitoring, working memory and executive function] and measurement of cerebral metabolite ratios using magnetic resonance spectroscopy (MRS) at baseline and week 48 (performed at 3 voxel locations: right frontal white matter, mid-frontal grey matter, and the right basal ganglia).	

Main outcomes:

	Arm I (n=114)	Arm II (n=105)	Arm III (n=103)
Death	2 (accidental electrocution and autoimmune haemolytic anaemia)	0	0
Loss to follow up/withdrew consent	1	1	9
Remained in follow-up	111	104	94
Cessation and/or modifications of ART	rash (*n*=3) and neurological	jaundice (*n*=5)	gastrointestinal disorders (*n*=17) and anemia

	symptoms (*n*=3)		(*n*=7)
discontinuations attributed to TDF-FTC	0	0	0
mean reductions in TWAUC (ITT pop'n)	2.59 logs	2.67 logs	2.39 logs

Other outcomes:

	Arm I vs. Arm II	Arm I vs. Arm III	Arm II vs. Arm III
Mean difference in TWAUC (ITT population)	0.08 (95% CI -0.08 to +0.23), p=0.323	-0.20 (95% CI -0.39 to -0.01), p=0.038	-0.28 (95% CI, -0.46 to -0.10), *P*=0.003)
Mean difference in TWAUC (PP population)	0.02 (95% CI -0.16 to +0.19), p=0.829	-0.25 (95% CI -0.45 to -0.05), p=0.014	-0.27 (95% CI, -0.46 to -0.08), *P*=0.007)

Week 48:

HIV-1 RNA threshold	Arm I (EFV/TDF)	Arm II (ATV/TDF)	Arm III (ZDV/ABC/TDF)	p value Arm I vs. Arm II	p value Arm I vs. Arm III
<50 copies/mL ITT*	97/108 (90%)	93/101 (92%)	75/98 (76%)	0.446	0.017
<50 copies/mL PP	82/88 (93%)	81/87 (93%)	60/64 (94%)	0.755	0.367
<200 copies/mL ITT	108/114 (95%)	101/105 (96%)	85/103 (82%)	0.750	0.005
<200 copies/mL PP	93/93 (100%)	89/91 (98%)	64/67 (96%)	0.243	0.077
<400 copies/mL ITT	109/114 (95%)	102/105 (97%)	85/103 (82%)	0.723	0.002
<400 copies/mL PP	93/100 (93%)	89/91 (98%)	64/67 (96%)	0.243	0.072

*14 patients at one site excluded due to lower limit of detection of HIV-RNA viral load assay 80 copies/mL

There were no differences in time to plasma HIV-RNA <200 copies/mL for either Arm II (*n*=105) or Arm III (*n*=97), compared with Arm I (*n*=111) (Arm I vs Arm II HR, 0.86; 95% CI, 0.66–1.13; and Arm I vs Arm III HR, 0.95; 95% CI, 0.72–1.24).
In the ITT population with confirmed HIV-RNA <200 copies/mL, 17 pts in Arm III rebounded to >200 copies/mL. This occurred at a significantly greater rate in Arm III, compared with the rate in Arm I (*n*=6) (HR, 3.30; 95% CI, 1.03–8.37; *P*=.012), although the rate in Arm II (*n*=5) was not significantly different from the rate in Arm I (HR, 0.88; 95% CI, 0.27–2.89; *P*=.840). Results were consistent for other HIV RNA thresholds and the PP population.

Variable	Arm I EFV/TDF-FTC (*n*=114)	Arm II r/ATV/TDF-FTC (*n*=105)	Arm III ZDV/ABC/TDF-FTC (*n*=103)
No. of adverse events (48 weeks)	495	409	485
No. of pts with adverse event	99	95	91
No. of adverse events ≥grade 3	25	35	32

No. of serious adverse events	15	15 (Arm I vs Arm II, *P*=0.922)	30 (Arm I vs Arm III, *P*=0.062)
No. of pts with ≥1 SAE	14	8	12
immune reconstitution inflammatory syndrome (IRIS)	14	17	21
mean change from baseline CD4+ cell count	187 cells/mL	192 cells/mL (Arm I vs Arm II, *P*=0.814)	163 cells/mL (Arm I vs Arm III, *P*=0.217)
Virologic failure	4	4	11
No. with resistance data available:	3	3	7
RT inhibitor mutations	2	1	2
Protease inhibitor mutations	1	0	4

There were no significant differences between treatment arms in quality of life; stress, anxiety, and depression score; or timed gait test result from week 0 to week 48 in both ITT and PP populations (data not shown).

Winston substudy

	Arm 1 (EFV/TDF)			Arm 2 (ATV/TDF)			Arm 2 vs arm 1	Arm 3 (ZDV/ABC/TDF)			Arm 3 vs arm 1
Cognitive domain:	No.	Mean	SD	No.	Mean	SD	Change [a] (95% CI), p	No.	Mean	SD	Change [a] (95% CI), p
Detection[b] log10 ms											
Baseline	9	2.51	0.13	8	2.56	0.16	-.513 [-1.501 to 0.475] .30	11	2.57	0.11	-0.717 (-1.631 to 0.197) .12
Week 48	9	2.55	0.18	8	2.55	0.10		12	2.54	0.13	
Identification[b] log10 ms											
Baseline	9	2.72	0.12	8	2.76	0.08	-0.681 (-1.635 to 0.273) 0.15	11	2.75	0.07	-0.908 (-1.791 to -0.026) 0.04
Week 48	9	2.75	0.14	8	2.73	0.06		12	2.70	0.05	
Monitoring[b] log10 ms											
Baseline	9	2.58	0.10	8	2.66	0.10	-0.809 (-1.793 to 0.175) 0.10	11	2.60	0.10	-0.288 (-1.198 to 0.623) 0.51
Week 48	9	2.57	0.11	8	2.60	0.11		12	2.58	0.07	
Learning (matched),[b] log10 ms											
Baseline	9	2.82	0.09	8	2.83	0.04	-0.290 (-1.288 to 0.708) 0.56	11	2.83	0.05	-0.652 (-1.576 to 0.271) 0.27
Week 48	9	2.83	0.15	8	2.83	0.05		12	2.80	0.06	
One card learning[c] arcsine											

Baseline	9	2.58	0.10	8	2.66	0.10	-0.046 (-1.060 to 0.969) 0.93	11	2.60	0.10	0.383 (-0.538 to 1.304) 0.40
Week 48	9	2.57	0.11	8	2.60	0.11		12	2.58	0.07	
Working memory[c] arcsine											
Baseline	9	1.08	0.36	8	1.17	0.21	-0.057 (-1.094 to 0.981) 0.91	11	1.09	0.44	0.105 (-0.854 to 1.065) 0.82
Week 48	9	1.18	0.30	8	1.25	0.15		12	1.22	0.14	
Associate learning[c] arcsine											
Baseline	9	0.82	0.26	8	0.99	0.17	0.240 (-0.793 to 1.274) 0.64	11	0.86	0.16	0.229 (-0.727 to 1.185) 0.63
Week 48	9	0.81	0.24	8	1.03	0.13		12	0.89	0.23	
Executive function[d] total no. of errors											
Baseline	9	43.44	27.86	8	47.38	18.55	-0.259 (-1.652 to 1.134) 0.71	11	56.36	27.69	-1.539 (-2.828 to -0.251) 0.02
Week 48	9	48.44	21.83	8	48.63	18.28		11	39.09	22.61	
Composite speed score, log10 ms											
Baseline	9	2.66	0.10	8	2.70	0.08	-0.785 (-1.729 to 0.158) 0.10	11	2.69	0.07	-0.939 (-1.812 to -0.066) 0.04
Week 48	9	2.68	0.08	8	2.68	0.07		12	2.65	0.06	
Composite accuracy score, arcsine											
Baseline	9	0.88	0.23	8	1.02	0.15	0.055 (-0.974 to 1.084) 0.91	11	0.91	0.24	0.362 (-0.635 to 1.268) 0.50
Week 48	9	0.92	0.18	8	1.06	0.15		12	0.99	0.12	

a Changes assessed using the methodology recommended by CogState. In brief, changes in standardized scores were weighted by the pooled standard deviation (SD) and entered into a linear regression model with the arm as a categorical covariate. Coefficient of change represents the mean difference for each treatment group compared to arm 1, and P values are the pairwise comparative significance tests.

b Used to determine speed; a lower score represents an improved response.

c Used to determine correct responses (i.e. accuracy of response); a higher score represents an improved response.

d A lower score represents an improved response.

	Arm 1			Arm 2			Arm 2 vs arm 1	Arm 3			Arm 3 vs arm 1
Voxel:	No.	Mean	SD	No.	Mean	SD	Change [a] (95% CI), p	No.	Mean	SD	Change [a] (95% CI), p
Front white matter: NAA/Cr ratio											
Baseline	7	1.860	0.280	9	1.834	0.269	-0.777 (-1.519 to -0.036) 0.041	12	1.924	0.436	-0.686 (-1.385 to 0.014) 0.054
Week 48	7	2.481	1.115	9	1.677	0.174		12	1.859	0.646	
Front white matter: Cho/Cr ratio											

Baseline	7	1.107	0.168	9	1.159	0.283	-0.116 (-0.450 to 0.219) 0.483	12	1.243	0.400	-0.103 (-0.419 to 0.213) 0.508
Week 48	7	1.168	0.183	9	1.105	0.133		12	1.201	0.195	
Front white matter: MI/Cr ratio											
Baseline	7	3.854	1.761	9	3.803	1.092	1.065 (-0.842 to 2.972) 0.261	12	3.881	1.994	1.513 (-0.297 to 3.322) 0.097
Week 48	6	2.595	1.581	9	3.729	0.770		12	4.255	1.596	
Frontal grey matter: NAA/Cr ratio											
Baseline	8	1.561	0.286	9	1.539	0.166	-0.120 (-0.758 to 0.517) 0.701	12	1.637	0.286	-0.295 (-0.894 to 0.303) 0.320
Week 48	9	1.919	0.357	9	1.814	0.953		12	1.737	0.312	
Frontal grey matter: Cho/Cr ratio											
Baseline	8	0.714	0.146	9	0.705	0.179	0.047 (-0.130 to 0.225) 0.587	12	0.657	0.137	0.045 (-0.121 to 0.212) 0.580
Week 48	9	0.688	0.161	9	0.724	0.171		12	0.674	0.149	
Frontal grey matter: MI/Cr ratio											
Baseline	6	3.268	1.804	9	3.247	0.857	-0.253 (-1.754 to 1.249) 0.731	12	2.774	1.017	-0.160 (-1.606 to 1.285) 0.821
Week 48	8	2.997	1.662	9	2.970	1.422		11	2.646	1.400	
Right basal ganglia: NAA/Cr ratio											
Baseline	7	1.908	0.431	8	2.274	0.976	-0.427 (-1.893 to 1.038) 0.552	12	1.921	0.340	-0.150 (-1.467 to 1.167) 0.815
Week 48	8	2.723	1.477	7	2.782	0.824		12	2.612	1.032	
Right basal ganglia: Cho/Cr ratio											
Baseline	7	0.974	0.183	8	1.225	1.121	-0.347 (-1.121 to 0.427) 0.363	12	0.893	0.186	0.139 (-0.557 to 0.835) 0.683
Week 48	8	0.910	0.235	7	0.875	0.188		12	0.976	0.381	
Right basal ganglia: MI/Cr ratio											
Baseline	6	3.268	1.804	9	3.247	0.857	-0.016 (-1.446 to 1.414) 0.982	12	2.774	1.017	0.099 (-1.218 to 1.416) 0.877
Week 48	7	3.219	1.452	7	3.001	0.907		11	2.604	0.708	

No statistically significant differences between changes in neurocognitive testing results and study treatment arms I versus II were observed, and none of the associations described differed when excluding subjects with a detectable plasma HIV-1 RNA level at week 48 or correcting for age in a sensitivity analysis. In a multivariate model, absolute change in the NAA/Cr ratio over 48 weeks was statistically significantly greater in arm 1 versus arm 2 (coefficient -0.789 (95% CI -1.516 to -0.063), *P*=.03). No other factors, including ethnicity, age, or detectable plasma HIV-1 RNA level, at week 48 were associated with these changes (*P* > .15 for all comparisons). Finally, no significant associations were observed between changes in cerebral metabolite ratios and neurocognitive testing results.

Authors' conclusion

A novel quadruple nucleo(t)side combination demonstrated significantly less suppression of HIV replication, compared with the suppression demonstrated by standard antiretroviral therapy regimens and safety performance. Efavirenz and ritonavir-boosted atazanavir arms were equivalent in viral suppression and safety. In the Winston substudy, greater improvements in neuronal recovery (NAA/Cr ratio) were observed for recipients of tenofovir-emtricitabine plus efavirenz (arm 1), and greater improvements in neurocognitive function testing were observed for recipients of tenofovir-emtricitabine plus zidovudine-abacavir (arm 3).

Reference	**Study type and methodological quality**	**No. pts**	**Patient characteristics**	**Intervention**	**Comparison**	**Follow-up**	**Outcome measures**	**Funding**
ACTG5202: Sax *et al.* Abacavir–Lamivudine versus Tenofovir–Emtricitabine for Initial HIV-1 Therapy. New Engl J Med 2009; 361(23): 2230-40 (ClinicalTrials.gov number, NCT00118898). Sax *et al.* Abacavir/ Lamivudine Versus Tenofovir DF/ Emtricitabine as Part of Combination Regimens for Initial	**RCT** **Allocation to treatment** Random Method of randomisation: Allocation used a centralized computer system. Randomization was stratified according to the screening HIV-1 RNA level obtained before study entry (≥ 100,000 vs. <100,000 copies per milliliter), with the use of a permuted-block design with dynamic balancing according to	**Total N: 1858** **First analysis includes data from the 797 patients with a screening HIV-1 RNA level of 100,000 copies per milliliter or more.** 718 patients (90%) remained in the study.	**INCLUSION CRITERIA** HIV-1–infected pts who were at least 16 years of age, who had received at most 7 days of antiretroviral therapy previously, and who had acceptable laboratory values. **EXCLUSION CRITERIA** pregnant or breastfeeding; were using immune-modulators; had any known allergies to the study drugs; abused substances	**Drug(s):** 300mg tenofovir DF plus 200mg emtricitabine (Truvada) (plus 600mg efavirenz or 300mg atazanavir plus 100mg ritonavir) **n=399 in first sub-group analysis**	**Drug(s):** 600mg abacavir plus 300 mg lamivudine (plus 600mg efavirenz or 300mg atazanavir plus 100mg ritonavir) **n=398 in first sub-group analysis (HIV-1 RNA**	**Treatment duration:** planned and actual study duration 96 weeks **Assessments at:** before entry, at entry, at weeks 4, 8, 16, and 24, and	**Primary endpoint:** time from randomization to virologic failure (a confirmed HIV-1 RNA level ≥1000 copies/ ml at or after 16 wks and before 24 wks, or ≥ 200 copies /ml at or after 24 wks) Other endpoints: Time from initiation of treatment to 1st grade 3 or 4 sign, symptom, or lab abnormality that was at least one grade higher than that at baseline, excluding isolated	Abbott Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, and GlaxoSmithKline provided the study medications and

Treatment of HIV: Final Results. J Infect Dis 2011; 204: 1191–201. Daar ES et al. Atazanavir Plus Ritonavir or Efavirenz as Part of a 3-Drug Regimen for Initial Treatment of HIV-1 A Randomized Trial. Ann Intern Med 2011; 154: 445-456. McComsey GA et al. Bone Mineral Density and Fractures in Antiretroviral-Naive Persons Randomized to Receive Abacavir-Lamivudine or Tenofovir Disoproxil Fumarate-Emtricitabine Along With Efavirenz or Atazanavir-Ritonavir: AIDS	the main institution Concealment: adequate **Blinding** double blinded with regard to NRTIs **Sample size calculation** Regimens were considered equivalent if the two-sided 95% confidence interval for the hazard ratio was between 0.71 and 1.40. A planned sample size of 1800 subjects (450 per group) would provide an 89.8% probability of declaring equivalence if two regimens were the same, assuming uniform accrual, exponential virologic failure, and lost-to-follow-up time distributions among the four groups, with event probabilities of 17.46% and 10.00%, respectively, at 48 weeks. Study conduct	Follow-up was discontinued in 41 patients assigned to abacavir–lamivudine and in 38 patients assigned to tenofovir DF–emtricitabine, with no significant difference in the distributions of time to discontinuation (P = 0.91). **Second analysis: low screening HIV RNA stratum (n=1060)**	that would interfere with the study; had a serious illness; had an important cardiac conduction disorder; required prohibited medications; showed evidence of major resistance mutations; were incarcerated; or, as of July 2006, had hepatitis B. Resistance testing was required for recently infected pts. **Baseline comparability between groups**: yes **Age**: median 38 years (IQR 31-45) **Gender**: 83% male **Severity of disease:** median CD4 cell count 229.5cells/ml (IQR 89.5-333.8)	**(HIV-1 RNA levels of 100 000 copies/mL or more at screening)** **n=530 in second sub-group analysis (HIV-1 RNA levels < 100 000 copies/mL at screening)** A5224s was a substudy of AIDS Clinical Trials Group (ACTG) A5202:	**levels of 100 000 copies/mL or more at screening)** **n=530 in second sub-group analysis (HIV-1 RNA levels < 100 000 copies/mL at screening)** A5224s was a substudy of AIDS Clinical Trials Group (ACTG) A5202: for n in each	every 12 weeks thereafter **Follow-up after end of treatment:** none **Median follow-up first analysis:** 60 weeks (range 0-112 weeks); **full analysis:** 136 weeks Median (25th, 75th percentile) **final** (Daar 2011) follow-	unconjugated hyper-bilirubinemia and elevations in the creatine kinase level, while the pt was receiving the randomly assigned treatment. Adverse events Coprimary objectives of A5224s were to compare effects of starting ABC-3TC with those of TDF/FTC on spine and hip BMD and on body fat. A5224s 2ry objectives were to compare BMD changes between EFV and ATV/r arms, to compare TDF-FTC with ABC-3TC and EFV with ATV/r on BMD changes at wk 48, and to compare % with bone fractures. Substudy evaluations included whole-body dual-energy X-ray absorptiometry (DEXA) scans at	had input into the protocol development and review of the manuscript.

Clinical Trials Group A5224s, a Substudy of ACTG A5202. J Infect Dis 2011; 203: 1791-801. McComsey GA et al. Peripheral and Central Fat Changes in Subjects Randomized to Abacavir Lamivudine or Tenofovir-Emtricitabine With Atazanavir-Ritonavir or Efavirenz: ACTG Study A5224s. Clinical Infectious Diseases 2011; 53(2): 185–196.	and safety data were reviewed yearly by the data and safety monitoring board. Efficacy data were reviewed annually starting with the second review of study data. Early stopping guidelines for inferiority were prespecified, with a regimen considered to be inferior if the 99.95% two-sided confidence interval for the hazard ratio for virologic failure did not include 1.0. **ITT analysis** Yes **Setting:** Outpatients		Specific A5224s exclusion criteria were uncontrolled thyroid disease or hypogonadism; endocrine diseases, including Cushing's syndrome, diabetes mellitus, and the use of growth hormone, anabolic steroids, glucocorticoids, or osteoporosis medications; or the intent to start bone-related treatment.	for n in each group see results section	group see results section	up was **138 weeks** (106 weeks, 169 weeks)	baseline and weeks 24, 48, 96, 144, and 192 and a single-slice abdomen CT scan at the L4-L5 level at baseline and week 96. Fat distribution was measured by DEXA in antero-posterior view (with use of Hologic or Lunar scanners). Technicians were instructed to use the same machine on the same subject throughout the study. CT was used to quantify visceral adipose tissue (VAT) and total adipose tissue (TAT).	

Patient disposition (data from both Sax publications)

Total (n=1857)							
High HIV RNA stratum (n=797)				Low HIV RNA stratum (n=1060)			
TDF/FTC (n=399)		ABC/3TC (n=398)		TDF/FTC (n=530)		ABC/3TC (n=530)	
with EFV (n=199)	with ATV (n=200)	with EFV (n=199)	with ATV (n=199)	with EFV (n=265)	with ATV (n=265)	with EFV (n=266)	with ATV (n=264)
VF*: 11/199 (6%)	15/200 (8%)	25/199 (13%)	32/199 (16%)	33/265 (12%)	29/265 (11%)	39/266 (15%)	35/264 (13%)
26/399		57/398		62/530		74/530	

*VF=virological failure
Combining high and low strata: TDF/FTC

All (n=1857)			
EFV (n=929)		ATV (n=928)	
with TDF (n=464)	with ABC (n=465)	with TDF (n=465)	with ABC (n=463)
VF: 44/464	64/465	44/465	67/463
108/929		111/928	

The data and safety monitoring board (DSMB) met on January 29, 2008, for the first efficacy review. Protocol prespecified time-to-event distributions were presented overall and within each screening HIV-1 RNA stratum. The DSMB noted excess virologic failures in both groups of pts who received regimens containing abacavir–lamivudine; additional requested analyses showed that these excess failures associated with abacavir–lamivudine occurred within the higher screening HIV-1 RNA stratum. When data in the four groups were combined and analyzed as two groups (i.e., the group receiving regimens with abacavir–lamivudine and the group receiving regimens without abacavir–lamivudine), the difference between these two groups was determined to be highly statistically significant. The DSMB found the strength and validity of these findings sufficient to warrant stopping the further study of abacavir–lamivudine among participants with a screening HIV-1 RNA level of at least 100,000 copies/mL. The board specified that the remainder of the study should continue without change.
On release of these findings from the DSMB, the study team completed additional analyses based on a previous analysis plan. Treatment-effect modification was assessed for six prespecified baseline covariates: sex, race or ethnic group, age, HIV-1 RNA level, CD4 cell count, and available or unavailable test results for HIV-1 genotype at screening.

First analysis includes data from the 797 patients with a screening HIV-1 RNA level of 100,000 copies/mL or more (high stratum).

High stratum	tenofovir DF–emtricitabine group (n=399)	abacavir–lamivudine group (n=398)	hazard ratio (HR), confidence interval (CI), p value
Protocol-defined virologic failure	26 patients	57 patients	
Time to virologic failure			HR 2.33; 99.95% CI 1.01 to 5.36; 95% CI, 1.46 to 3.72; P<0.001
Estimated probability of remaining free of virologic failure beyond 48 weeks	0.93 (95% CI 0.90 to 0.96)	0.84 (95% CI 0.79 to 0.88)	HR 2.08 (95% CI 1.28 to 3.37)

The relative hazard of virologic failure between the NRTI groups according to the six baseline covariates (univariate analysis) showed significant

treatment interactions with sex (P = 0.04), available or unavailable genotype information at screening (P = 0.02), and baseline CD4 cell count (P = 0.007). Tenofovir DF–emtricitabine treatment was associated with a lower rate of virologic failure than abacavir–lamivudine among men, pts with a screening genotype result, and pts with a lower baseline CD4 cell count. When a multivariable model was fitted with these baseline factors, the differences in the hazard ratios for failure remained significant for male sex (P = 0.05), available genotype information (P = 0.03), and lower CD4 cell count (P = 0.01).

Other outcomes:

CD4 cell count distributions and the change from baseline were similar in the two groups. At week 48, the median increase from baseline was 194 cells/mm^3 (interquartile range, 126 to 305) in the 248 pts assigned to abacavir–lamivudine and 199 cells/ mm^3 (IQR 129 to 302) in the 248 pts assigned to tenofovir DF–emtricitabine (P = 0.78).

High HIV RNA stratum	tenofovir DF–emtricitabine (n=399)	abacavir–lamivudine (n=398)	hazard ratio, CI, p value
at least one grade 3 or 4 sign, symptom, or laboratory abnormality that was at least one grade higher than the baseline value, while receiving their initial regimen	78	130	
grade 4 event	13	24	
time to the safety end point			1.89; 95% CI, 1.43 to 2.50; P<0.001
week 48 median change in total cholesterol level	26mg/dl	34mg/dl	P<0.001
week 48 median change in HDL cholesterol level	7mg/dl	9mg/dl	P=0.05
week 48 median change in triglyceride level	3mg/dl	25mg/dl	P = 0.001
median change in total: HDL cholesterol ratio	−0.2	−0.2	P = 0.50
Suspected study drug–related hypersenstivity	27 (7%)	27 (7%); 1 died	
Subsequent virologic failure among patients with suspected drug hypersensitivity	3	4	
AIDS events	17 (4%)	26 (7%)	
HIV-related cancers	4	8	
Bone fractures	10	7	
Myocardial infarctions	0	0	
Renal failure	2	2	
median change from baseline in calculated creatinine	2ml/min (IQR −11 to	4ml/min (IQR −7 to	P = 0.10

clearance	16); n=241	16); n=212	

Among the 81 patients with resistance data that could be evaluated, major reverse-transcriptase or protease resistance mutations at baseline were detected in 5 patients randomly assigned to abacavir–lamivudine and 4 randomly assigned to tenofovir DF–emtricitabine. Emergence of major drug-resistance mutations was noted in 25 patients in the abacavir–lamivudine group (6% of those randomly assigned to the group and 45% of group members with virologic failure) and in 10 patients in the tenofovir DF–emtricitabine group (3% and 38%, respectively). Among the 35 patients with the emergence of new major resistance mutations at the time of virologic failure, 3 in each group had other major mutations at baseline.

Main (final results Sax 2011) publication:

	TDF/FTC	ABC/3TC	Comparisons between TDF and ABC groups: Hazard ratio, CI, p value or difference	p value for difference between ATV and EFV
NRTI comparison combined across ATV/r and EFV regimens (factorial analysis) for all patients (high and low HIV RNA stratum): virologic failure	**88/929**	**131/928**	HR 1.70 (95% CI 1.23, 2.35)	
combining high and low HIV RNA strata (with ATV/r)	44/465	67/463	HR 1.48 (95% CI, 0.95, 2.31)	p=0.38
combining high and low HIV RNA strata (with EFV)	44/465	64/465	HR 1.98 (95% CI 1.22, 3.20)	
high HIV RNA stratum: virologic failure (with ATV/r)	15/200	32/199	HR 2.22 (95% CI, 1.19, 4.14)	p=0.82
high HIV RNA stratum: virologic failure (with EFV)	11/199	25/199	HR 2.46 (95% CI, 1.20, 5.05)	
low HIV RNA stratum: virologic failure (with ATV/r)	29/265 (11%)	35/264 (13%)	HR 1.25 (95% CI 0.76, 2.05)	
low HIV RNA stratum: virologic failure (with EFV)	33/265 (12%)	39/266 (15%)	HR 1.23 (95% CI, 0.77, 1.96)	

CD41 Cell Count Changes in the Low HIV RNA Stratum
Among those on ATV/r, there was no significant difference in distribution of change from baseline CD41 cells/mm^3 between ABC/3TC and TDF/FTC at week 48 (week 96); median 170 ABC/3TC and 157 TDF/FTC (240 ABC/3TC and 241 TDF/FTC), P > 0.6 for both time points. Among those on EFV, ABC/3TC recipients experienced significantly greater CD41 cells/mm^3 increases compared with TDF/FTC at weeks 48 and 96 (median 175 vs 147, P = .035; and 227 vs 200, P = .035, respectively).

Tolerability Endpoints in the Low HIV RNA Stratum

Low HIV RNA stratum	tenofovir DF–emtricitabine (n=530)	abacavir–lamivudine (n=530)	hazard ratio, CI, p value

time to first antiretroviral drug modification			ATV/r: HR 1.43 (95% CI, 1.06, 1.92, P = .018); EFV: HR 1.48 (95% CI, 1.12, 1.95, P = .005).
time to first modification of the NRTIs			ATV/r: HR 1.57 (95% CI 1.14, 2.16, P = .006); ETV: HR 1.84 (95% CI 1.36, 2.51, P < .0001)
unblinding of NRTIs for suspected drug hypersensitivity ATV/r EFV severe hypersensitivity reaction when rechallenged	 11 (4 renal) 8 (5 renal) 1	 23 32 0	
Safety event Time to first safety event with ATV/r Time to first safety event with EFV			 HR 1.13; 95% CI 0.83 to 1.54 P=.44 HR 1.38; 95% CI, 1.03, 1.85, P = .03
Death with ATV with EFV	 0 3 (bacterial pneumonia, stroke, Mycobacterium avium complex)	 4 (non-Hodgkin's lymphoma, MI, car accident, drug overdose/ suicide) 3 (bladder carcinoma, hepatic carcinoma, unknown)	
Cardiovascular events with ATV/r with EFV	34 15/265 (6%) 19/265 (7%)	29 15/264 (6%) 14/266 (5%)	
Bone fractures with ATV/r with EFV	 10/265 (4%) 13/265 (5%)	 7/264 (3%) 15/266 (6%)	
Site-reported incidence of renal disease with ATV/r with EFV	 7/265 (3%) 5/265 (2%)	 10/264 (4%) 10/266 (4%)	

Data on change from baseline in calculated creatinine clearance to weeks 48 and 96 were available for the 75% and 66% of patients who started study regimen, respectively. Statistically significant improvements from baseline to weeks 48 and 96 was found within all treatment arms (all P = .018) at both time points, except for ATV/r with TDF/FTC group at week 96 (P = .14). With ATV/r, there were significant differences in the distribution of change from baseline calculated creatinine clearance between ABC/3TC and TDF/FTC at both week 48 (median +3.3 vs -3.1 mL/min, P < .001) and week 96 (median +5.2 mL/min vs -3.1 mL/min, P < .001). For EFV with ABC/3TC vs TDF/FTC, there was no significant difference in the change from baseline in calculated creatinine clearance at week 48 (median +2.6 mL/min vs +3.3 mL/min, P = .83) or week 96 (+7.0 mL/min vs +4.5 mL/min, P = .15). For patients on a randomized treatment regimen with fasting samples (range 154–188 patients per treatment arm), changes from baseline in lipids levels were generally greater with ABC/ 3TC than TDF/FTC. With ATV/r, median changes for ABC/3TC vs TDF/FTC at week 48 respectively were total cholesterol, 30 vs 8 mg/dL (P < .001); low-density lipoprotein (LDL) cholesterol, 14 vs 0 mg/dL (P < .001); high-density lipoprotein (HDL) cholesterol, 7 vs 4 mg/dL (P< .001); and triglycerides, 27 vs 14 mg/dL (P = .004). With EFV, changes in total cholesterol were 34 vs 19 mg/dL (P < .001); LDL cholesterol, 17 vs 6 mg/dL (P <.001); HDL cholesterol, 12 vs. 9 mg/dL (P = .006); and triglycerides, 12 vs 13 mg/dL (P= .49), respectively. There was no significant difference between NRTIs in the change in the total:HDL cholesterol ratio. Results were similar at week 96.

Selected Events That Triggered a Safety Endpoint While Receiving Randomized Antiretroviral Drugs in Low Screening HIV RNA Stratum

	ABC (n = 263)	TDF (n = 265)	ABC (n = 264)	TDF (n = 263)	All subjects (n = 1055) who started medication
	ATV/r		EFV		
Overall, n (%)	80 (30)	98 (37)	78 (29)	83 (32)	339 (32)
Metabolic, n (%)	22 (8)	19 (7)	24 (9)	13 (5)	78 (7)
Total cholesterol (fasting), n	4	1	9	4	
LDL (fasting), n	7	7	15	8	
Triglycerides (fasting), n	8	3	5	0	
Glucose (nonfasting)	2	5	0	1	
Gastrointestinal, n (%)	21 (8)	16 (6)	12 (5)	12 (5)	61 (6)
Diarrhoea/loose stool, n.	2	4	8	2	
ALT, n	7	1	1	6	
Nausea and/or vomiting, n	6	3	3	1	
Neuropsychological, n (%)	8 (3)	1 (<1)	16 (6)	14 (5)	39 (4)
Depression, n.	3	0	3	7	
General body, n (%)	29 (11)	30 (11)	42 (16)	30 (11)	131 (12)
Ache/pain/discomfort, n	20	11	12	17	

Fever, n	6	7	6	1	
Asthenia/fatigue, n	3	3	7	3	
Rash/allergic reaction, n	2	2	5	2	
Headache, n	3	3	6	1	
Hematologic, n (%)	1 (<1)	7 (3)	4 (2)	7 (3)	19 (2)
Neutrophil count, n	1	6	4	7	

In the low HIV RNA stratum, 136 ps had virologic failure, with resistance data available at baseline and failure in all but 2 pts. Baseline major resistance was present in 13 (10%) pts with virologic failure. Among 122 virologic failures with no major resistance at baseline, there was no significant difference in the occurrence of major resistance mutations between ABC/3TC and TDF/FTC when given with either ATV/r or EFV. Resistance data for pts in the high HIV RNA stratum with virologic failure at the time of the DSMB review showed that when given with ATV/r, the emergence of major NRTI resistance mutations was not significantly different with ABC/3TC (6 of 29) or TDF/FTC (3 of 14, P=1.0 of failures and P=.34 of randomized). With EFV, major NRTI resistance emerged in 15/23 and 2/8 randomized to ABC/3TC and TDF/FTC, respectively (P = .10 of failures and P = .002 of randomized).

Daar 2011 Publication:

Summary of Primary End Points at Baseline, 96 Weeks, and Full Follow-up, With Efavirenz as the Reference in All Comparisons

Variable	Abacavir–Lamivudine		Tenofovir DF–Emtricitabine	
	Efavirenz	Atazanavir Ritonavir	Efavirenz	Atazanavir Ritonavir
Time to virologic failure				
Baseline Persons at risk, n	465	463	464	465
96 wk Events/persons at risk (Kaplan–Meier estimate), n/n (%)	63/331 (14.7)	72/338 (16.6)	44/367 (10.2)	48/364 (11.0)
Difference in 96-wk Kaplan–Meier estimate (95% CI), percentage points	1.9 (2.9 to 6.8)		0.8 (3.3 to 4.9)	
Full follow-up Events/total person-years at risk, n/n	72/1011.7	83/1017.1	57/1095.6	57/1086.4
Estimated HR (95% CI)	1.13 (0.82 to 1.56) NB no difference by viral load stratum (p=0.147)		1.01 (0.70 to 1.46) NB no difference by viral load stratum (p=0.37)	
Time to primary safety end point (First grade-3 or -4 sign,				

symptom, or laboratory abnormality while receiving the originally assigned third drug (atazanavir/ritonavir or efavirenz) that was ≥1 grade higher than baseline, excluding isolated unconjugated hyperbilirubinemia and creatine kinase)				
Baseline Persons at risk, n	461	462	461	464
96 wk Events/persons at risk (Kaplan–Meier estimate), n/n (%)	175/176 (41.7)	152/229 (35.5)	126/248 (30.2)	119/268 (27.7)
Difference in 96-wk Kaplan–Meier estimate (95% CI), percentage points; P value	6.2 (12.9 to 0.4); 0.066		2.5 (8.6 to 3.7); 0.43	
Full follow-up Events/total person-years at risk, n/n	187/631.2	170/762.5	147/814.3	141/868.9
Estimated HR (95% CI); P value	0.81 (0.66 to 1.00); 0.048 no difference in effect by viral load stratum (*P* = 0.71)		0.91 (0.72 to 1.15); 0.44 no difference in effect by viral load stratum (*P* = 0.85)	
Time to AIDS or death	HR, 0.93 [CI, 0.56 to 1.54]; *P* = 0.77		HR, 1.23 [CI, 0.70 to 2.39]; *P* =0.42	
Time to primary tolerability end point (First change in therapy, ignoring nucleoside reverse transcriptase inhibitors)				
Baseline Persons at risk, n	461	462	461	464
96 wk Events/persons at risk (Kaplan–Meier estimate), n/n (%)	155/290 (33.7)	110/334 (23.9)	114/328 (24.8)	97/347 (21.0)
Difference in 96-wk Kaplan–Meier estimate (95% CI), percentage points; P value	9.8 (15.6 to 4.0); 0.001		3.8 (9.2 to 1.6); 0.170	
Full follow-up Events/total person-years at risk, n/n	186/943.7	142/1052.6	142/1032.1	126/1088.5
Estimated HR (95% CI); P value	0.69 (0.56 to 0.86); <0.001 no difference by viral load stratum (*P* = 0.63)		0.84 (0.66 to 1.07); 0.166 no difference by viral load stratum (*P* = 0.90).	

A prespecified comparison of atazanavir plus ritonavir and efavirenz with NRTIs combined (factorial analysis) was done because there was no evidence that the treatment effect differed by NRTIs (P = 0.65). For atazanavir plus ritonavir versus efavirenz, the HR for time to virologic failure was 1.08 (CI, 0.85 to 1.38), with CIs within the prespecified equivalence boundaries. However, for this comparison, there was a significant interaction with screening viral load (P = 0.080), in which the HRs were 1.35 (CI, 0.96 to 1.92) and 0.88 (CI, 0.62 to 1.23) for the high and low viral load stratum, respectively.

	abacavir–lamivudine			tenofovir DF–emtricitabine		
	ATZ/r	efavirenz	difference	ATZ/r	efavirenz	difference
Pts with HIV-1 RNA levels <50 copies/mL (regardless of previous virologic failure or regimen change) of the 1642 (88%) and 1498 (81%) of patients with HIV-1 RNA results available at week 48 and week 96, respectively*	n not stated	n not stated		n not stated	n not stated	
Week 48**	78%	87%	8 percentage points [CI, 13 to 3]; P = 0.03	84%	90%	6 percentage points [CI, 11 to 1]; P = 0.012
Week 96**	85%	91%	6 percentage points [CI, 11 to 1]; P =0.012	90%	91%	difference, 1 percentage point [CI, 5 to 3]; P =0.58
Time to 1st confirmed virologic failure or discontinuation of assigned PI or NNRTI			HR, 0.87 [CI, 0.71 to 1.08]			HR, 0.93 [CI, 0.74 to 1.17]

*Data were missing primarily because of premature discontinuation of the study (e.g. pt moved, was incarcerated, was deported) or the pt was lost to follow-up. Patients with missing data were more likely than persons with results to be younger, to be a non-Hispanic black person, to report previous intravenous drug use, and to have hepatitis B or C infection.

**In a prespecified, worst-case sensitivity analysis, in which patients with missing data were assigned to the group with HIV-1 RNA levels of 50 copies/mL or more, 48-week results were similar to primary analyses, and at 96 weeks, abacavir–lamivudine no longer favored efavirenz.

Change in CD4 cell counts from baseline to weeks 48 and 96 was examined in 1645 (89%) and 1493 (80%) of patients with results available, respectively. Reasons for missing CD4 values were similar to reasons noted for HIV-1 RNA. Change in CD4 cell counts did not differ between persons given atazanavir plus ritonavir or efavirenz with abacavir–lamivudine, with a median change of 0.178 versus 0.188 x 10^9 cells/L (*P* = 0.94) and 0.250 versus 0.251 x 10^9 cells/L (*P* = 0.89), respectively. Change in CD4 cell count was greater in persons given atazanavir plus ritonavir than those given efavirenz with tenofovir DF–emtricitabine at weeks 48 and 96, with a median change of 0.175 versus 0.163 x 10^9 cells/L (*P* = 0.040) and 0.252 versus 0.221 x 10^9 cells/L (*P* = 0.002), respectively. n not stated

Safety events

	Abacavir–Lamivudine	**Tenofovir DF–emtricitabine**

	Efavirenz (n = 461)	**Atazanavir/ Ritonavir (n = 462)**	**Efavirenz (n = 461)**	**Atazanavir/ Ritonavir (n = 464)**
Death, n (Of the 1857 randomly assigned patients)	11	8	6	6
Selected primary safety end point event, n (%): overall	187 (41)	170 (37)	147 (32)	141 (30)
Fasting total cholesterol level	21	11	7	2
Fasting LDL cholesterol level	29	14	15	7
Fasting triglycerides level	17	16	5	7
Blood glucose level	4	7	2	4
Gastrointestinal	23 (5)	38 (8)	22 (5)	25 (5)
AST	6	14	6	6
ALT	5	13	9	5
Diarrhoea or loose stools	11	7	6	6
Nausea, vomiting, or both	5	8	2	3
Neuropsychological	28 (6)	14 (3)	28 (6)	10 (2)
Depression	6	4	13	5
Dizzy or lightheaded	6	0	2	2
Insomnia, dreams, or sleep	6	0	5	0
General	71 (15)	64 (14)	46 (10)	59 (13)
Ache, pain, or discomfort	25	35	23	21
Fever	10	16	4	12
Asthenia, fatigue, or malaise	8	5	7	8
Headache	10	7	3	6
Rash or allergic rash	9	3	4	6
Vascular events (coronary artery disease, infarction, ischemia, angina, CVA, TIA or peripheral vascular disease)	2 (<1%)	2 (<1%)	6 (1%)	1 (<1%)
Renal diagnoses of the Fanconi syndrome, toxic nephropathy, proteinuria, or renal failure	5 (1%)	4 (1%)	3 (1%)	6 (1%)
bone fractures	22 (5%)	16 (3%)	21 (5%)	21 (5%)
suspected hypersensitivity reaction	53 (11%)	34 (7%)	25 (5%)	27 (6%)

Of the 269 patients with protocol-defined virologic failure, 265 had resistance data available at failure and baseline; of these, 25 had major mutations at baseline. Among patients with virologic failure, emergent resistance mutations were less frequent in those assigned to received atazanavir plus

ritonavir than in those assigned to receive efavirenz, combined with either NRTI (*P* < 0.001 for both). There was also a lower frequency of NRTI-associated mutations among persons assigned to receive atazanavir plus ritonavir than those assigned to receive efavirenz with abacavir–lamivudine (*P* < 0.001) or tenofovir DF–emtricitabine (*P* = 0.046).

	Abacavir–Lamivudine		**Tenofovir DF–emtricitabine**	
	Efavirenz (n = 461)	**Atazanavir/ Ritonavir (n = 462)**	**Efavirenz (n = 461)**	**Atazanavir/ Ritonavir (n = 464)**
Virologic failure Events, *n (%)*	72 (15)	83 (18)	57 (12)	57 (12)
Genotype available at failure Major mutations at baseline Without mutations at baseline	71 8 63	83 7 76	55 7 48	57 3 54
Mutations, n (%) [%] *				
Any major mutation	41 (9) [65]	12 (3) [16]	27 (6) [56]	5 (1) [9]
NRTI-associated	25 (5) [40]	11 (2) [14]	11 (2) [23]	5 (1) [9]
NNRTI-associated	41 (9) [65]	1 (<1) [1]	27 (6) [56]	0 (0) [0]
NRTI + NNRTI-associated	25 (5) [40]	0 (0) [0]	11 (2) [23]	0 (0) [0]
Protease-associated (N88N/S)	0 (0) [0]	1 (<1) [1]	0 (0) [0]	0 (0) [0]

*Excludes patients with major resistance mutations present at baseline but includes 1 person who had resistance data available at virologic failure but not at baseline. Total may not add up to 100% because some patients had >1 mutation. Values are total number (percentage of persons randomly assigned) [percentage of persons with a genotype and without baseline resistance]

A5224s substudy of AIDS Clinical Trials Group (ACTG) A5202 (McComsey bone paper)

	Efavirenz + TDF (n =69)	**Efavirenz + ABC (n = 70)**	**Atazanavir/ Ritonavir + TDF (n = 65)**	**Atazanavir/ Ritonavir + ABC (n = 65)**
Median age (IQR)	40 (33-44)	39 (31-46)	38 (30-44)	37 (29-43)
Male	58 (84%)	56 (80%)	56 (86%)	59 (91%)
Median (IQR) CD4 cells/µL	250 (132-334)	213 (106-350)	247 (114-319)	222 (75-332)
Median (IQR) lumbar spine BMD (g/cm^2)	1.12 (1.00-1.23)	1.08 (.97-1.23)	1.13 (1.03-1.24)	1.13 (1.04-1.23)
Median (IQR) hip BMD (g/cm^2)	0.99 (.92-1.07)	1.02 (.93-1.11)	1.05 (.98-1.18)	1.02 (.97-1.13)

Mean (SD) change in lumbar spine BMD (%), week 0-96	-2.52 (4.08), n=54, p<0.001	-0.78 (5.20), n=53, p=0.28	-4.38 (4.95), n=43, p<0.001	-1.99 (4.69), n=48, p=0.005
Mean (SD) change in hip spine BMD (%), week 0-96	-3.69 (3.81), n=54, p<0.001	-2.54 (4.40), n=51, p<0.001	-4.31 (5.17), n=42, p<0.001	-2.68 (3.30), n=48, p<0.001

The estimated mean % change in spine BMD for all participants was 23.0% at week 48 and 22.3% at week 96. The comparison of ABC-3TC (n = 135) and TDF-FTC (n = 134) with EFV and ATV/r combined (factorial analysis) was performed, because there was no significant evidence that the treatment effect between these drugs differed at 96 weeks by the NNRTI-PI component (P = .63). Similarly, the comparison of EFV (n = 139) and ATV/r (n = 130) with ABC-3TC and TDFFTC combined was performed.

Changes by NRTI Components: Primary Analysis.

By ITT at week 96, there was a significant decrease in mean % change in spine BMD for all arms except ABC-3TC plus EFV, but significantly less for ABC-3TC (estimated mean of -1.3%) than for TDF-FTC (-3.3%; difference [Δ] = 2.0%; 95% confidence interval [CI], 0.7%–3.3%; P = .004).

At wk 96, among pts assigned to receive EFV, there was a trend toward a greater decrease in mean % change in spine BMD when combined with TDF-FTC than when combined with ABC-3TC (Δ, 1.7%; 95% CI, .04%–3.5%; P = .056). In ATV/r-treated arms, there was a significantly greater decrease in mean % change in spine BMD when combined with TDF-FTC than when combined with ABC/3TC (Δ, 2.4%; 95% CI, .4%–4.4%; P = .020, by ITT).

Changes by NNRTI-PI Component: Secondary Analysis.

At week 96, by ITT analysis, the mean % change in spine BMD was significantly greater in those assigned to ATV/r (-3.1%) than in those in the EFV arm (-1.7%; Δ, -1.5%; 95% CI, 22.8% to 2.1%; P = .035).

Changes by NRTI Components: Primary Analysis.

At wk 96, ITT analysis showed that the ABC-3TC arms had a significantly smaller decrease in mean % change in hip BMD, compared with the TDF-FTC arms (-2.6% vs -4.0%; Δ, 1.4%; 95% CI, .2%–2.5%; P = .024). For persons assigned to receive EFV, at 96 wks, the mean % change in hip BMD was not significantly different between the NRTI components, compared with those assigned to receive ABC-3TC; the estimated mean change was -2.5%, compared with -3.7% for those given TDF-FTC (Δ, 1.2%; 95% CI, 2.4% to 2.7%; P = .15). There was a trend toward a smaller decrease in mean % change in hip BMD for persons given ATV/r with ABC-3TC (-2.7%), compared with those given TDF-FTC (-4.3%; Δ, 1.6%; 95% CI, .2%–3.4%; P = .075).

Changes by NNRTI-PI Component: Secondary Analysis.

At week 96 and by ITT analysis, the mean % change in hip BMD was not statistically significantly different between EFV and ATV/r (Δ, -.3%; 95% CI, -1.5% to .9%; P = .61).

The ITT analyses of mean % change from entry to wk 96 of spine and hip BMD were adjusted for the following prespecified baseline covariates that could affect BMD, first individually and then jointly, with use of linear regression: NNRTI-PI (or NRTI components for the NNRTI-PI analyses), spine BMD (or hip BMD for corresponding analysis), sex, age, race/ethnicity, $\log_{10}$ HIV-1 RNA load, CD4 cell count, and BMI. For analyses of the NRTI component effect or the NNRTI-PI component effect, all of the adjusted models led to results similar to those of the unadjusted analyses. In the 96-week

percentage change in lumbar spine BMD, multivariable analysis, ABC-3TC (vs TDF-FTC) p=0.003 and ATV/r (vs EFV) p=0.039 were significant and in the 96-week percentage change in hip BMD, multivariable analysis, ABC-3TC (vs TDF-FTC) was significant p=0.033.

Bone fractures: EFV: 10; ATZ: 5. No significant difference between the NRTIs (P = 1.00) or the NNRTI and PI study arms (P = .29). Similarly, there was no statistically significant difference in time to first bone fracture between NRTI (P = .76) or NNRTI/PI study arms (P = .27). In the parent study-A5202, 80 participants (4.3%) reported at least one bone fracture on study (ABC-3TC plus EFV, 4.7%; ABC-3TC plus ATV/r, 3.5%; TDF-FTC plus EFV, 4.5%; and TDF-FTC plus ATV/r, 4.5%). Among these, 10 (12.7%) were atraumatic. The bone fractures were balanced across the study arms, with no statistically significant differences between the NRTI (P = .73) or the NNRTI and PI components (P = .57). No statistically significant difference in time to first bone fracture was seen between the NRTIs (P=.71) or the NNRTI and PI components (P = .49). Similarly, incidence rates were similar across arms (ABC-3TC plus EFV, 1.9/100 pt-years; ABC-3TC plus ATV/r, 1.4/100 pt-years; TDF-FTC plus EFV, 1.8/100 pt-years; and TDF-FTC plus ATV/r, 1.8/100 pt-years).

Overall, 66 (25%) of the A5224s pts prematurely discontinued the substudy, and 4 (1%) died. In addition, 31 pts (12%) discontinued because their sites were defunded during the study. There was no significant difference in time to premature study discontinuation between NRTI components (P = .13, site closure and death censored) or NNRTI-PI components (P = .86). The median time from randomization to the last clinic visit was 165 weeks.

McComsey lipodystrophy paper

Variable	EFV/ TDF-FTC (n = 56)	EFV /ABC-3TC (n = 53)	ATV-r/ TDF-FTC (n = 45)	ATV-r / ABC-3TC (n = 49)
No. pts with ≥ 10% limb fat loss	8	10	7	8
Prevalence of ≥ 10% limb fat loss (primary analysis), % (95% CI)	14.3 (6.4–26.2)	18.9 (9.4–32.0)	15.6 (6.5–29.5)	16.3 (7.3–29.7)
No. pts with ≥ 20% limb fat loss	5	2	0	3
Prevalence of ≥ 20% limb fat loss (post hoc analysis), % (95% CI)	8.9 (3.0–19.6)	3.8 (0.5–13.0)	0.0 (0.0–7.9)	6.1 (1.3–16.9)
Mean (SD) change in limb fat (%) week 0–96	15.3 (36.7), n=56, p=0.003	17.7 (30.7), n=53, p<0.001	27.8 (36.4), n=45, p<0.001	32.7 (48.0), n=49, p<0.001
Mean (SD) change in trunk fat (%) week 0–96	20.1 (44.1), n=56, p=0.001	22.2 (44.6), n=53, p=0.001	35.9 (50.7), n=45, p<0.001	37.0 (58.3), n=49, p<0.001
Mean (SD) change in VAT (%) week 0–96	14.8 (48.7), n=54, p=0.03	9.9 (45.1), n=51, p=0.12	29.5 (88.4), n=45, p=0.031	23.7 (41.4), n=45, p<0.001
Mean (SD) change in VAT:TAT ratio (%) week 0–96	-0.2 (19.7), n=54, p=0.95	-1.9 (20.9), n=51, p=0.52	-2.2 (19.1), n=45, p=0.44	-2.3 (21.4), n=45, p=0.48

	combining the ATVr and EFV groups, within the **ABC-3TC** arms	combining the ATVr and EFV groups, within the **TDF-FTC** arms	difference, p value
prevalence (upper bound of 1-sided 95% confidence interval [CI]) of lipoatrophy	17.6% (25.0%)	14.9% (21.5%)	p=0.70
mean absolute and percentage changes in limb fat	1.66 kg and 24.9%	1.11 kg and 20.9%	difference (Δ) 0.55 kg (95%CI, -0.14 to 1.24; P = .12) and 4% (95% CI, -6.7% to 14.7%; P = .46)
mean absolute and percentage changes in trunk fat			Δ= 0.37 kg (95% CI, -0.58 to 1.32; P = .45) and 2.2% (95% CI, -11.6% to 15.9%; P = .76)
absolute and percentage changes in VAT and VAT:TAT ratio			-2.8 cm^2 (95% CI, -12.9 to 7.3; P = .58), -5.1% (95% CI, -21.5% to 11.4%; P = .55), and 0.00 (95% CI, -0.02 to 0.02; P=.94)
gains in mean BMI (post hoc endpoint)			Δ= 0.63 kg/m^2; 95% CI, -0.12 to 1.38; P = .099

In multivariable analysis, ABC vs. TDF (p=0.013), ATV vs. EFV (p=0.32) and number of copies of HIV RNA/mL (p<0.001) were significant for limb fat.

	combining ABC-3TC and TDF-FTC, within the **ATV-r** arms	combining ABC-3TC and TDF-FTC, within the **EFV** arms	difference, p value
mean absolute and percentage changes in limb fat	1.88 kg and 30.4%	0.96 kg and 16.5%	difference (Δ) 0.93 kg (95% CI, 0.24–1.61; P = .008) and 13.9% (95% CI, 3.3%–24.5%; P = .010)
mean absolute and percentage changes in trunk fat	2.42 kg; 36.5%	1.33 kg; 21.1 %	Δ= 1.09 kg (95% CI, 0.15–2.03; P = .023) and 15.4% (95% CI, 1.7%–29.0%; P = .028).
absolute and percentage changes from baseline in VAT and VAT:TAT ratio			Δ= 7.6 cm^2 (95% CI, -2.4 to 17.7; P = .14), 14.2% (95% CI, -2.2% to 30.6%; P = .090) and 0.00 (95% CI, -0.02 to 0.02; P = .92).

gains in mean BMI (post hoc endpoint)			Δ=0.88 kg/m^2; 95% CI, 0.13–1.62; P 5 .022

Authors' conclusion

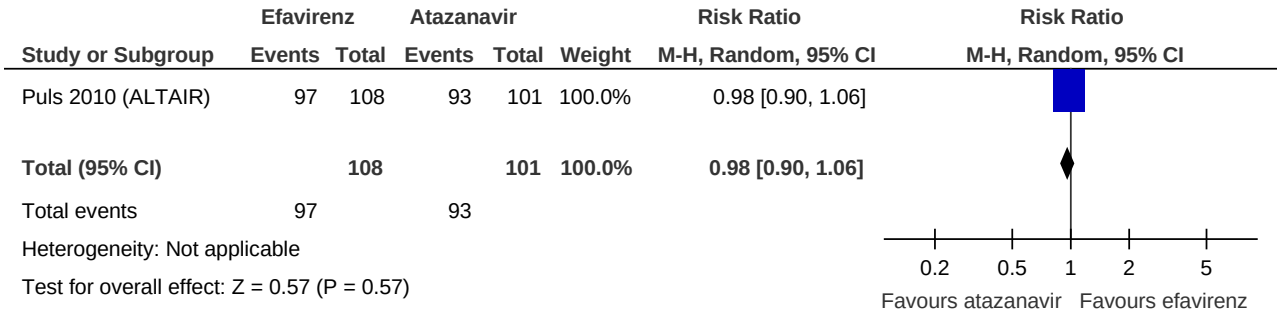
This large comparative clinical trial of ABC/3TC and TDF/FTC combined with either ATV/r or EFV found little difference in virologic efficacy between the 2 NRTI strategies when the screening HIV RNA was $<10^5$ copies/mL. By contrast, in the high RNA stratum, the time to virologic failure was faster with ABC/3TC than TDF/FTC with either ATV/r or EFV; furthermore, safety and tolerability generally favored TDF/FTC over ABC/3TC. Overall, these results support recent treatment guidelines that TDF/FTC be the preferred initial NRTI combination in treatment-naive patients, with ABC/3TC being an effective alternative choice. Several factors should be considered when selecting the optimal initial NRTI combination for an individual patient, including baseline HIV RNA level, HLA-B*5701 status, coinfection with hepatitis B, renal function, and lipid parameters.

At week 96, TDF-FTC, both in the spine and hip, and ATV/r in the spine produced significantly more bone loss than did ABC-3TC– or EFV-based regimens.

ABC-3TC– and TDF-FTC–based regimens increased limb and visceral fat at week 96, with a similar prevalence of lipoatrophy. Compared to the EFV group, subjects assigned to ATV-r had a trend towards higher mean percentage increase in VAT.

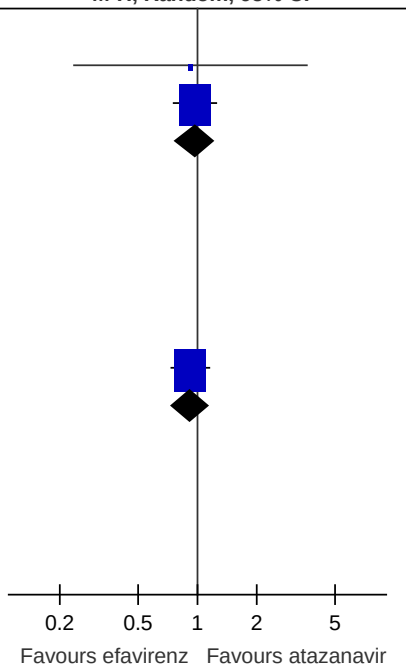
Forest plots

Forest plot of comparison: 1 Efavirenz versus atazanavir, outcome: 1.1 Viral suppression <50 copies week 48.



Forest plot of comparison: 1 Efavirenz versus atazanavir, outcome: 1.2 Virological failure.

Study or Subgroup	Efavirenz Events	Efavirenz Total	Atazanavir Events	Atazanavir Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Week 48						
Puls 2010 (ALTAIR)	4	114	4	105	3.2%	0.92 [0.24, 3.59]
Sax 2011 (ACTG 5202)	108	929	111	928	96.8%	0.97 [0.76, 1.25]
Subtotal (95% CI)		**1043**		**1033**	**100.0%**	**0.97 [0.76, 1.24]**
Total events	112		115			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						
1.2.2 Week 96						
Daar 2011 (ACTG 5202)	129	929	140	928	100.0%	0.92 [0.74, 1.15]
Subtotal (95% CI)		**929**		**928**	**100.0%**	**0.92 [0.74, 1.15]**
Total events	129		140			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.46)						

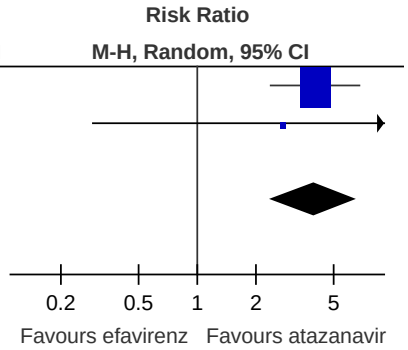


Forest plot of comparison: 1 Efavirenz versus atazanavir, outcome: 1.3 Drug resistance.

Study or Subgroup	Efavirenz Events	Efavirenz Total	Atazanavir Events	Atazanavir Total	Weight	Risk Ratio M-H, Random, 95% CI
Daar 2011 (ACTG 5202)	68	922	17	926	94.9%	4.02 [2.38, 6.78]
Puls 2010 (ALTAIR)	3	114	1	105	5.1%	2.76 [0.29, 26.15]
Total (95% CI)		**1036**		**1031**	**100.0%**	**3.94 [2.37, 6.56]**
Total events	71		18			

Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%

Test for overall effect: Z = 5.27 (P < 0.00001)

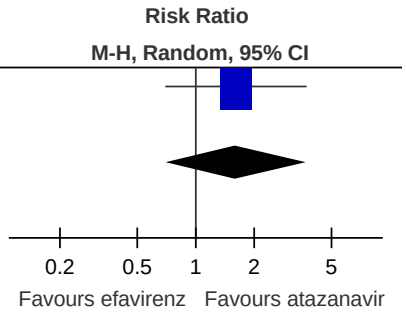


Forest plot of comparison: 1 Efavirenz versus atazanavir, outcome: 1.4 Serious adverse event.

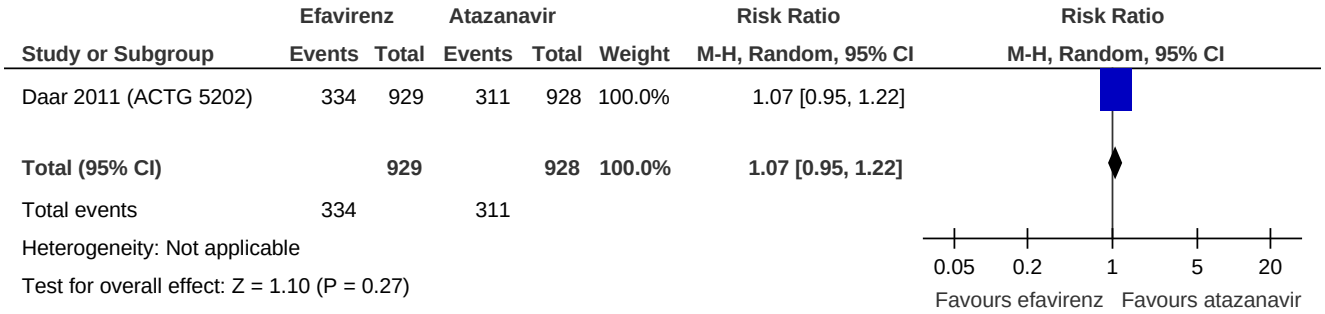
Study or Subgroup	Efavirenz Events	Efavirenz Total	Atazanavir Events	Atazanavir Total	Weight	Risk Ratio M-H, Random, 95% CI
Puls 2010 (ALTAIR)	14	114	8	105	100.0%	1.61 [0.70, 3.69]
Total (95% CI)		**114**		**105**	**100.0%**	**1.61 [0.70, 3.69]**
Total events	14		8			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.13 (P = 0.26)



Proportion with grade 3/4 adverse events



Quality of life

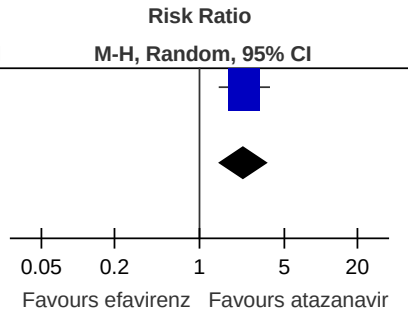
No data from these studies to address these outcomes.

Proportion with grade 3/4 neurological events

Study or Subgroup	Efavirenz Events	Total	Atazanavir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Daar 2011 (ACTG 5202)	56	922	24	926	100.0%	2.34 [1.47, 3.75]
Total (95% CI)		**922**		**926**	**100.0%**	**2.34 [1.47, 3.75]**
Total events	56		24			

Heterogeneity: Not applicable

Test for overall effect: Z = 3.56 (P = 0.0004)

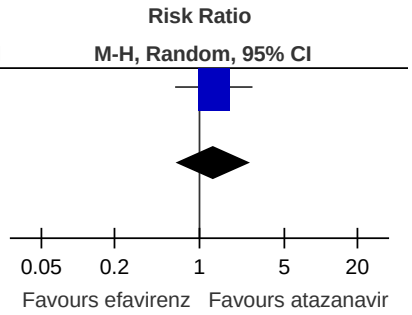


Proportion with grade 3/4 diarrhoea

Study or Subgroup	Efavirenz Events	Total	Atazanavir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Daar 2011 (ACTG 5202)	17	922	13	926	100.0%	1.31 [0.64, 2.69]
Total (95% CI)		**922**		**926**	**100.0%**	**1.31 [0.64, 2.69]**
Total events	17		13			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.75 (P = 0.46)



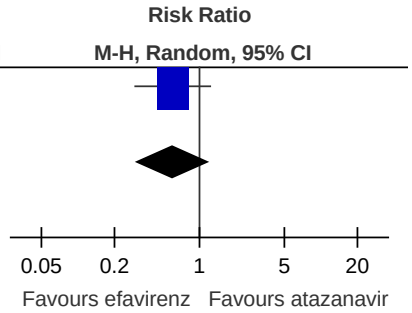
No clear evidence of a difference between the treatment arms.

Proportion with grade 3/4 AST elevation

Study or Subgroup	Efavirenz Events	Efavirenz Total	Atazanavir Events	Atazanavir Total	Weight	Risk Ratio M-H, Random, 95% CI
Daar 2011 (ACTG 5202)	12	922	20	926	100.0%	0.60 [0.30, 1.23]
Total (95% CI)		**922**		**926**	**100.0%**	**0.60 [0.30, 1.23]**
Total events	12		20			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.40 (P = 0.16)



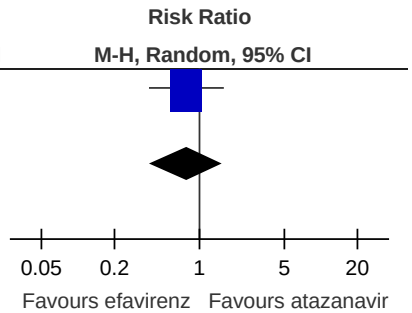
No clear evidence of a difference between the treatment arms.

Proportion with grade 3/4 ALT elevation

Study or Subgroup	Efavirenz Events	Efavirenz Total	Atazanavir Events	Atazanavir Total	Weight	Risk Ratio M-H, Random, 95% CI
Daar 2011 (ACTG 5202)	14	922	18	926	100.0%	0.78 [0.39, 1.56]
Total (95% CI)		**922**		**926**	**100.0%**	**0.78 [0.39, 1.56]**
Total events	14		18			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.70 (P = 0.48)

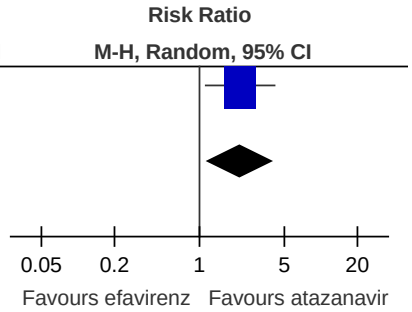


Proportion with grade 3/4 total cholesterol

Study or Subgroup	Efavirenz Events	Total	Atazanavir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Daar 2011 (ACTG 5202)	28	922	13	926	100.0%	2.16 [1.13, 4.15]
Total (95% CI)		**922**		**926**	**100.0%**	**2.16 [1.13, 4.15]**
Total events	28		13			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.32 (P = 0.02)

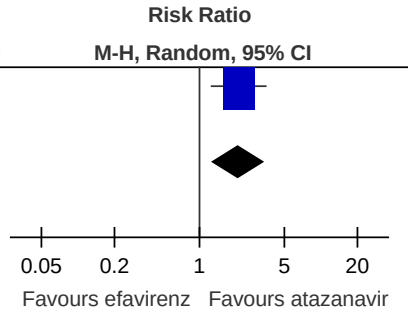


Proportion with grade 3/4 LDL cholesterol

Study or Subgroup	Efavirenz Events	Total	Atazanavir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Daar 2011 (ACTG 5202)	44	922	21	926	100.0%	2.10 [1.26, 3.51]
Total (95% CI)		**922**		**926**	**100.0%**	**2.10 [1.26, 3.51]**
Total events	44		21			

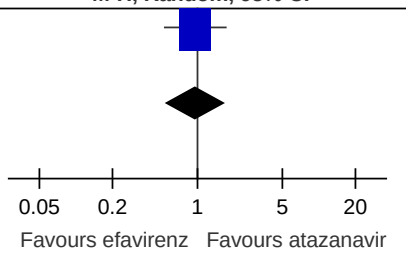
Heterogeneity: Not applicable

Test for overall effect: Z = 2.85 (P = 0.004)



Proportion with grade 3/4 triglycerides

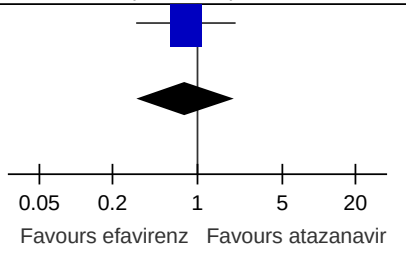
	Efavirenz		Atazanavir			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Daar 2011 (ACTG 5202)	22	922	23	926	100.0%	0.96 [0.54, 1.71]	
Total (95% CI)		**922**		**926**	**100.0%**	**0.96 [0.54, 1.71]**	
Total events	22		23				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.14 (P = 0.89)							



No clear evidence of a difference between the treatment arms.

Renal failure

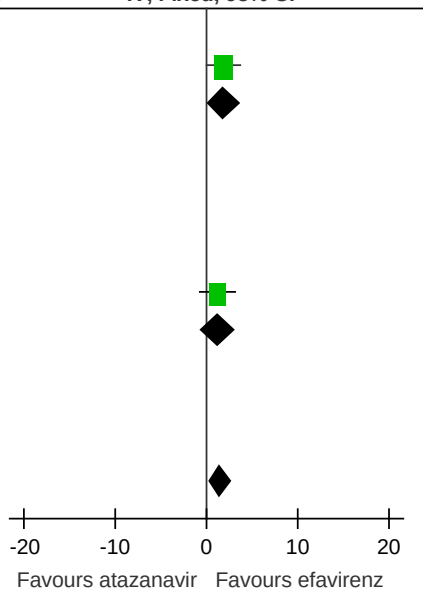
	Efavirenz		Atazanavir			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Daar 2011 (ACTG 5202)	8	922	10	926	100.0%	0.80 [0.32, 2.03]	
Total (95% CI)		**922**		**926**	**100.0%**	**0.80 [0.32, 2.03]**	
Total events	8		10				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.46 (P = 0.64)							



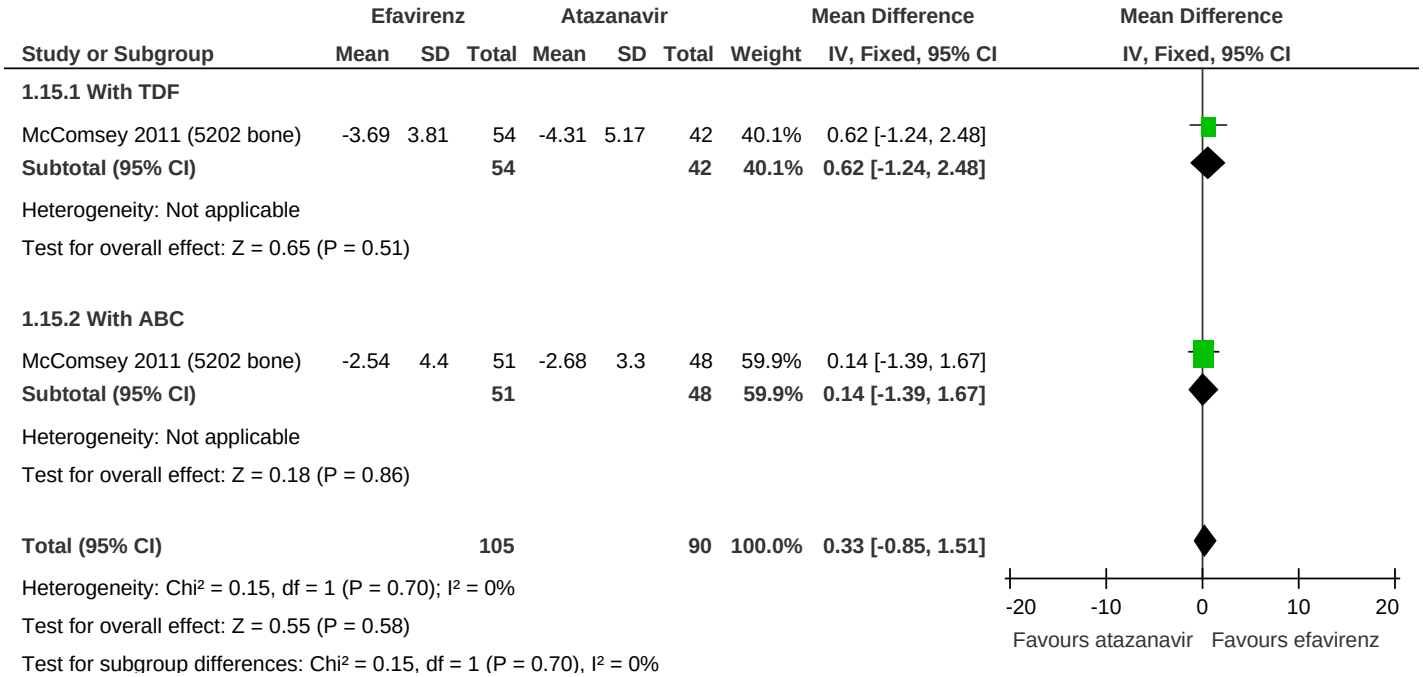
No clear evidence of a difference between the treatment arms.

Chronic toxicities (bone): Change in lumbar spine BMD (%, week 96).

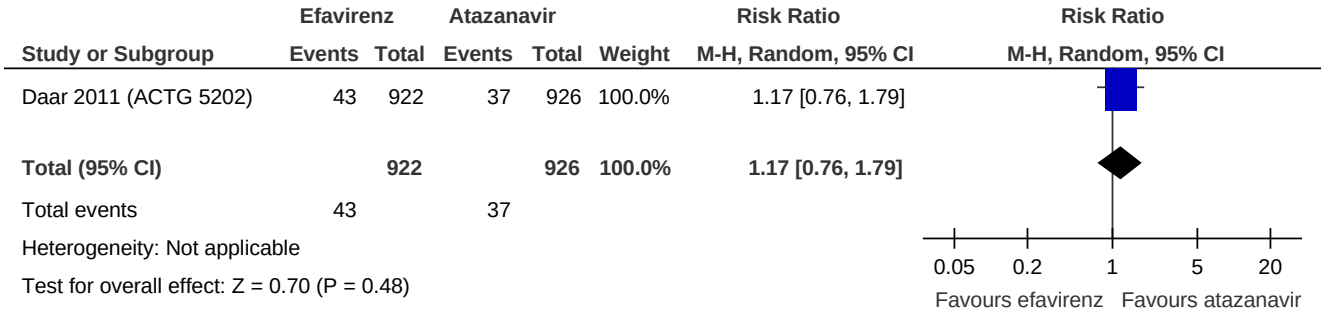
	Efavirenz			Atazanavir				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
1.14.1 With TDF									
McComsey 2011 (5202 bone)	-2.52	4.08	54	-4.38	4.95	43	52.4%	1.86 [0.02, 3.70]	
Subtotal (95% CI)			**54**			**43**	**52.4%**	**1.86 [0.02, 3.70]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.98 (P = 0.05)									
1.14.2 With ABC									
McComsey 2011 (5202 bone)	-0.78	5.2	53	-1.99	4.69	48	47.6%	1.21 [-0.72, 3.14]	
Subtotal (95% CI)			**53**			**48**	**47.6%**	**1.21 [-0.72, 3.14]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.23 (P = 0.22)									
Total (95% CI)			**107**			**91**	**100.0%**	**1.55 [0.22, 2.88]**	
Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² = 0%									
Test for overall effect: Z = 2.29 (P = 0.02)									
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%									



Change in hip BMD (%, week 96).



Bone fractures

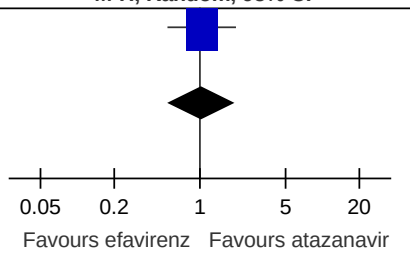


No clear evidence of a difference between the treatment arms.

Lipodystrophy outcomes

Patients with 10% or more limb fat loss (week 96).

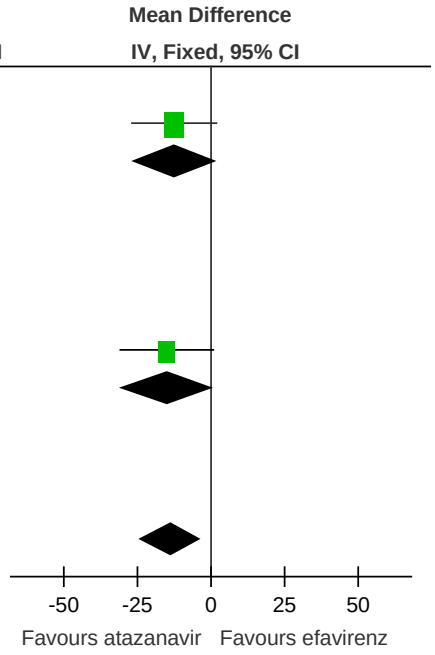
	Efavirenz		Atazanavir			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
McComsey 2011 (5202 lipo)	18	109	15	94	100.0%	1.03 [0.55, 1.94]	
Total (95% CI)		**109**		**94**	**100.0%**	**1.03 [0.55, 1.94]**	
Total events	18		15				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.11 (P = 0.91)							



Suggests no difference between groups.

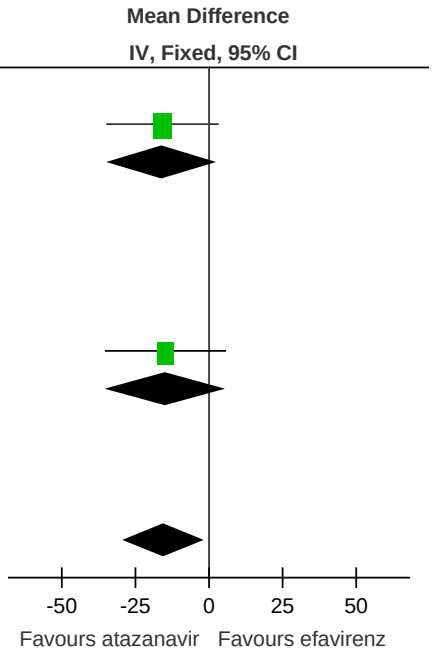
Change in limb fat (%, week 96).

Study or Subgroup	Efavirenz Mean	SD	Total	Atazanavir Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.18.1 With TDF								
McComsey 2011 (5202 lipo)	15.3	36.7	56	27.8	36.4	45	54.8%	-12.50 [-26.84, 1.84]
Subtotal (95% CI)			**56**			**45**	**54.8%**	**-12.50 [-26.84, 1.84]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.71 (P = 0.09)								
1.18.2 With ABC								
McComsey 2011 (5202 lipo)	17.7	30.7	53	32.7	48	49	45.2%	-15.00 [-30.78, 0.78]
Subtotal (95% CI)			**53**			**49**	**45.2%**	**-15.00 [-30.78, 0.78]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.86 (P = 0.06)								
Total (95% CI)			**109**			**94**	**100.0%**	**-13.63 [-24.24, -3.02]**
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%								
Test for overall effect: Z = 2.52 (P = 0.01)								
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%								

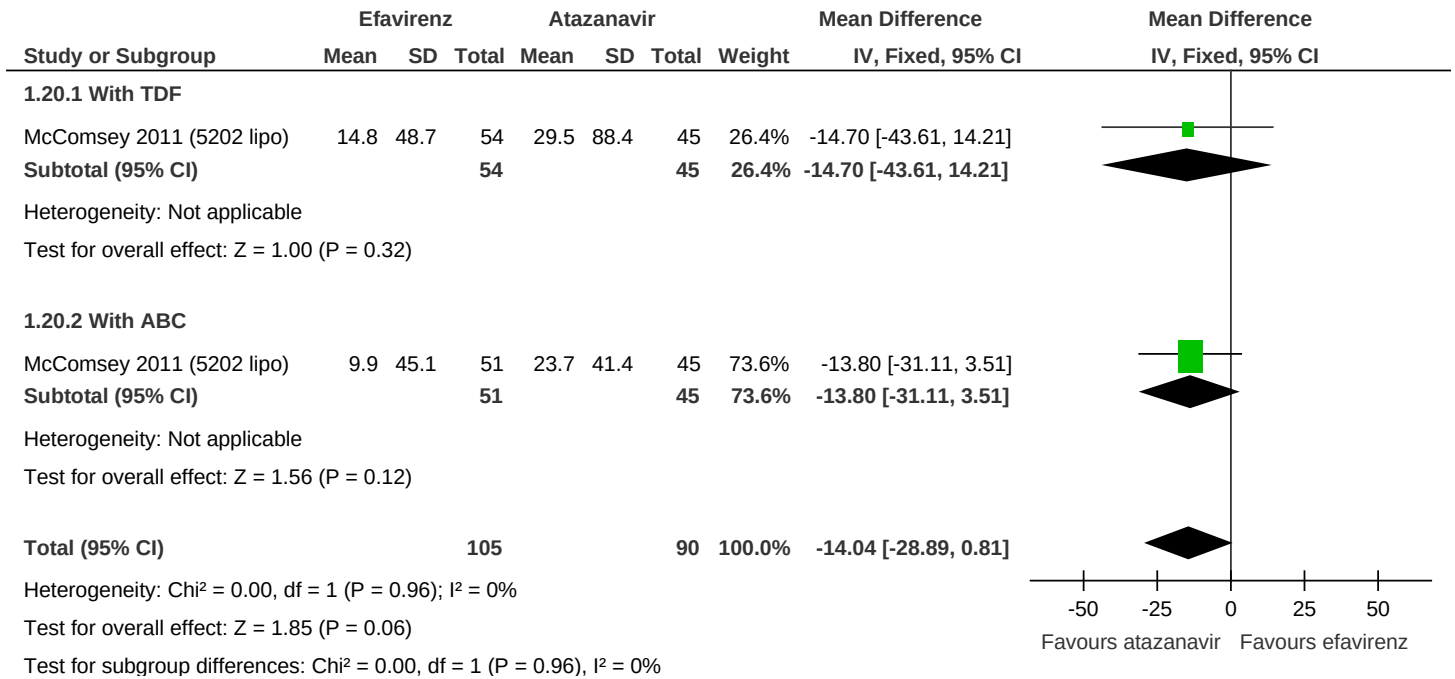


Change in trunk fat (%, week 96).

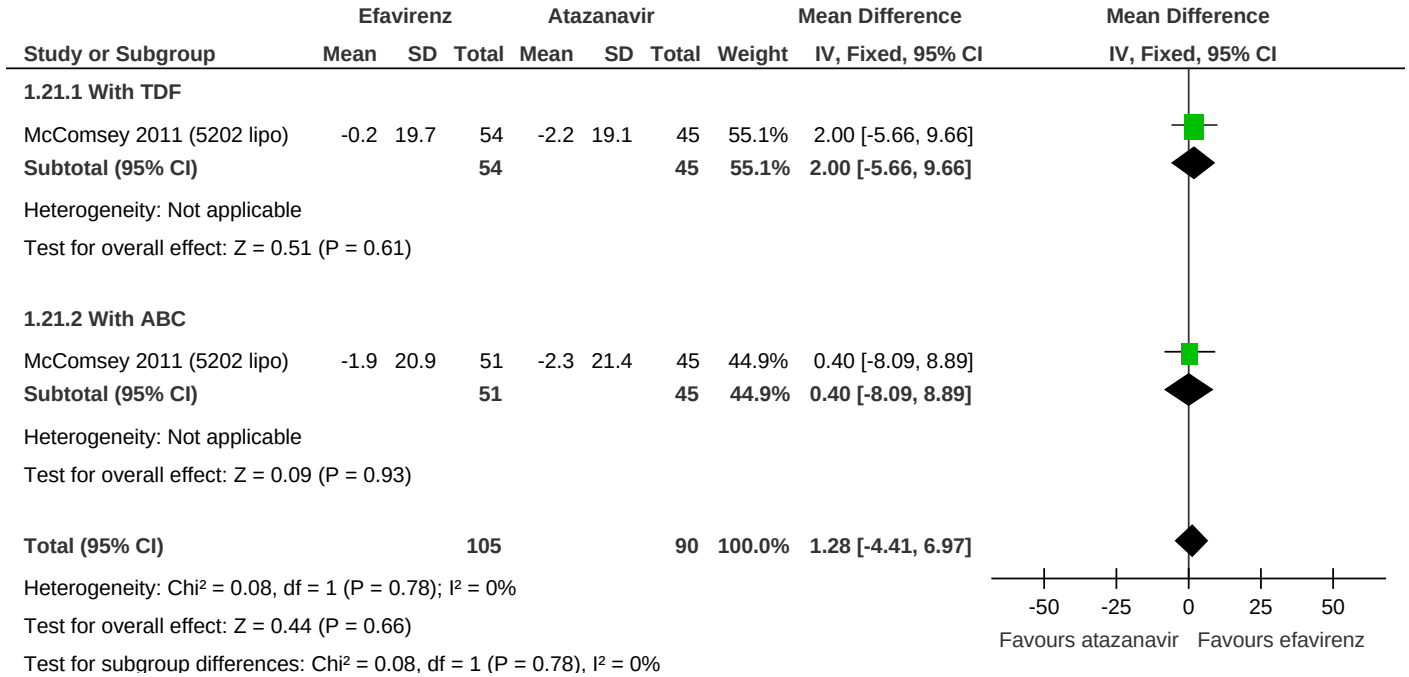
Study or Subgroup	Efavirenz Mean	SD	Total	Atazanavir Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.19.1 With TDF								
McComsey 2011 (5202 lipo)	20.1	44.1	56	35.9	50.7	45	53.8%	-15.80 [-34.58, 2.98]
Subtotal (95% CI)			**56**			**45**	**53.8%**	**-15.80 [-34.58, 2.98]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.65 (P = 0.10)								
1.19.2 With ABC								
McComsey 2011 (5202 lipo)	22.2	44.6	53	37	58.3	49	46.2%	-14.80 [-35.06, 5.46]
Subtotal (95% CI)			**53**			**49**	**46.2%**	**-14.80 [-35.06, 5.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.43 (P = 0.15)								
Total (95% CI)			**109**			**94**	**100.0%**	**-15.34 [-29.11, -1.56]**
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%								
Test for overall effect: Z = 2.18 (P = 0.03)								
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%								



Change in visceral adipose tissue (VAT; %, week 96).



Change in visceral: total adipose tissue (VAT:TAT; %, week 96).



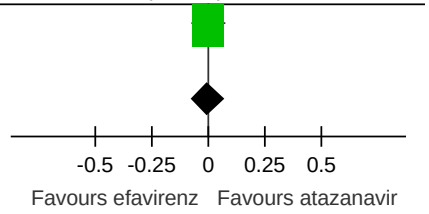
Cognitive outcomes

Cognitive speed score (lower = better).

	Efavirenz			Atazanavir				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Winston 2010 (ALTAIR sub)	2.68	0.08	9	2.68	0.07	8	100.0%	0.00 [-0.07, 0.07]	
Total (95% CI)			**9**			**8**	**100.0%**	**0.00 [-0.07, 0.07]**	

Heterogeneity: Not applicable

Test for overall effect: Z = 0.00 (P = 1.00)

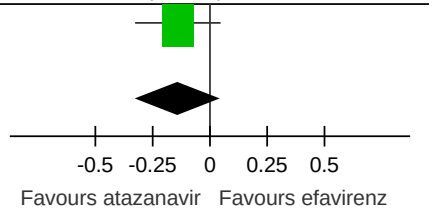


Cognitive accuracy score (higher = better).

	Efavirenz			Atazanavir				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Winston 2010 (ALTAIR sub)	0.88	0.23	9	1.02	0.15	8	100.0%	-0.14 [-0.32, 0.04]	
Total (95% CI)			**9**			**8**	**100.0%**	**-0.14 [-0.32, 0.04]**	

Heterogeneity: Not applicable

Test for overall effect: Z = 1.50 (P = 0.13)



NNT/NNH table for Efavirenz versus atazanavir

Efavirenz and atazanavir were **equally *effective*** (outcomes of viral suppression, virological failure).

The only significant differences between the drugs were for the following *safety* outcomes:

	Efavirenz better	Atazanavir better	ARR	NNT
Drug resistance	no	yes	51/1000	20
grade 3/4 neurological events	no	yes	35/1000	
grade 3/4 total cholesterol	no	yes	16/1000	
grade 3/4 LDL cholesterol	no	yes	25/1000	

20 people would need to be treated with atazanavir rather than efavirenz to avoid 1 case of drug resistance.

B Rilpivirine versus efavirenz

Two randomised trials were found comparing rilpivirine versus efavirenz:

- ECHO:
  - Molina JM et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. Lancet 2011; 378: 238–46.
- THRIVE:
  - Cohen CJ et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. Lancet 2011; 378: 229–37.

Reference	**Study type/ methodological quality**	**No. pts**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Funding**
Molina, J.-M., P. Cahn, et al. (2011). "Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3	**RCT:** Efficacy Comparison in Treatment-naive, HIV-infected Subjects of TMC278 and Efavirenz (ECHO) **Allocation to treatment** Random Method of randomisation: computer-	**Total N: 694; 50/346 rilpivirine discontinued (14.4 %) and 56/344 efavi**	**INCLUSION CRITERIA** pts aged 18 years or older, who had not been previously treated with antiretroviral drugs, a plasma viral load at screening of ≥5000 copies/mL, and viral sensitivity to tenofovir-disoproxil-fumarate and emtricitabine (assessed with the resistance genotype virco TYPE HIV-1 assay; Virco BVBA, Beerse, Belgium). **EXCLUSION CRITERIA** infection with HIV-2, documented evidence of at least one NNRTI resistance-associated mutation (RAM) from a list of 39 (A98G, L100I, K101E/P/Q,	**Drug(s):** rilpivirine 25mg daily + tenofovir-disoproxil-fumarate 300mg and emtricitabine 200mg **n=346**	**Drug(s):** efavirenz 600mg daily + tenofovir-disoproxil-fumarate 300mg and emtricitabine 200mg **n=348 (of whom 4 not**	**Treatment duration:** 96 weeks **Assessments at:** wks 2 and 4, every 4 wks until wk 16,	**Primary endpoint:** % of pts with confirmed response (according to the intention-to-treat time-to-loss-of virological-response [ITT-TLOVR] algorithm) at 48 wks (non-inferiority at a margin of 12%) Other endpoints: non-inferiority at a 10% margin, superiority (if non-inferiority was shown), durability of	Tibotec

randomised double-blind active-controlled trial." Lancet **378**(9787): 238-246	generated interactive web response system Concealment: adequate **Blinding** double blinded **Sample size calculation** yes **ITT analysis** Yes **Setting:** Outpatients	**renz (16.3 %)**	K103H/N/S/T, V106A/M, V108I, E138A/G/K/Q/R, V179D/E, Y181C/I/V, Y188C/H/L, G190A/C/E/Q/S/T, P225H, F227C, M230I/L, P236L, K238N/T, and Y318F), any active clinically significant disease (e.g. pancreatitis, cardiac dysfunction, active and significant psychiatric disorder, adrenal insufficiency, hepatic impairment), renal impairment (estimated glomerular filtration rate based on creatinine <50 mL/min), and, for women, pregnancy or breastfeeding. Disallowed drugs included those which could reduce exposure to rilpivirine (i.e. potent cytochrome 3A4-inducers and proton-pump inhibitors); drugs disallowed for efavirenz or tenofovir-disoproxil-fumarate and emtricitabine, as per the package inserts; any anti-HIV treatment other than drugs used in our trial; and all investigational drugs. **Baseline comparability between groups**: yes **Age**: median 36 (range 18‑78) yr on rilpivirine and 36 (19‑67) yr on efavirenz **Gender**: 78 (23%) female on rilpivirine		**treated)**	and then every 8 wks **Follow-up after end of treatment:** 4 weeks	antiviral activity, changes from baseline in CD4 cell count, safety, tolerability, HIV genotypic and phenotypic characteristics (in virological failures), adherence (measured with the Modified Medication Adherence Self-Report Inventory [M-MASRI]), pharmacokinetics, and pharmacokinetic and pharmacodynamic relations	

			and 69 (20%) on efavirenz **Severity of disease:** median CD4 cell count 240 (range 1‑888) on rilpivirine and257 (1‑757) cells/ml on efavirenz					

Main outcomes:

Week 48	**Rilpivirine**	**Efavirenz**	**% difference (95% CI)**
ITT-TLOVR outcome	N=346	N=344	
Viral load < 50 copies per mL	287 (83%)	285 (83%)	0.1 (-5.5 to 5.7)
VFeff =virological failure for the efficacy (ITT-TLOVR) endpoint: never suppressed [no confirmed response before week 48] rebounders [confirmed response before wk 48 with confirmed rebound ≤ wk 48]	38 (11%) 22 (6%) 16 (5%)	15 (4%) 7 (2%) 8 (2%)	
Discontinuation due to adverse events	6 (2%)	25 (7%)	
Discontinuation due to reason other than an adverse event (lost to follow-up, non-compliance, withdrew consent, ineligible to continue, or sponsor's decision)	15 (4%)	19 (6%)	
Model-predicted response (logistic regression (ITT-TLOVR outcome <50 copies per mL) adjusted for baseline viral load)	83%	84%	‑0.4 (‑5.9 to 5.2)
Per-protocol‑TLOVR outcome: number of assessable pts in each treatment group	335	330	
Viral load < 50 copies per mL	282 (84%)	275 (83%)	0.8 (‑4.8 to 6.5)

Other outcomes:

At week 48, mean change in absolute CD4 cell count from baseline was 196 cells per µL (95% CI 179‑212) for rilpivirine and 182 cells per µL (165‑198) for efavirenz (p=0.13).

Week 48	**Rilpivirine (n=346)**	**Efavirenz (n=344)**
VFres=virological failure established with the resistance analysis defined as any pt in the ITT population experiencing treatment failure irrespective of time of failure, treatment status, or reason for discontinuation providing the following criteria were met: never achieved two consecutive viral-load values of < 50 copies per mL and had an increase in viral load of 0.5 log10 copies per mL or greater above the nadir (never suppressed), or first achieved two consecutive viral-load values of < 50 copies per mL with two subsequent consecutive (or single, when last available) viral load values of ≥50 copies per mL (rebounder).	45 (13%)	19 (6%)

VFres with resistance data at time of failure	40	13
VFres with any treatment-emergent NNRTI RAM	26/40 (65%)	8/13 (62%)
VFres with any treatment-emergent IAS-USA N(t)RTI RAM	28/40 (70%)	4/13 (31%)
VFres with any treatment-emergent NNRTI or IAS-USA N(t)RTI RAM	29/40 (73%)	8/13 (62%)
NNRTI RAM incidence in patients who failed with NNRTI mutations (1 pt on efavirenz had V108I (8%), as did one pt on rilpivirine (3%))	n=26	n=8
E138K 18	(69%)	0
K101E 5	(19%)	0
Y181C 5	(19%)	0
V90I 4	(15%)	0
H221Y	4 (15%)	0
V189I	3 (12%)	0
E138Q	2 (8%)	0
K103N	0	7 (88%)
IAS-USA N(t)RTI RAM incidence in pts who failed with N(t)RTI mutations (K70E was reported in 1 pt in the rilpivirine group versus 0 pts in the efavirenz group)	n=28	n=4
M184I, V, or both	26 (93%)	4 (100%)
M184I only	20 (71%)	1 (25%)
M184V only	4 (14%)	2 (50%)
M184I/V mixtures	2 (7%)	1 (25%)
K65R	3 (11%)	0
K219E	3 (11%)	0
Y115F	2 (7%)	0

Adverse events

	Rilpivirine N=346	**Efavirenz N=344**	**p value**
Median treatment duration (weeks; range)	56 (0-87)	56 (1-88)	
Any adverse event	303 (88%)	317 (92%)	
Any treatment-related adverse event of grade 2 or greater	55 (16%)	108 (31%)	<0.0001
Adverse event leading to permanent discontinuation	8 (2%)	27 (8%)	
Any serious adverse event (including death)	23 (7%)	31 (9%)	

Death	0	1 (0%)	
Most common treatment-related adverse event of grade 2 or greater in ≥2% of pts in either group (excluding laboratory abnormalities reported as an adverse event)			
Dizziness	4 (1%)	23 (7%)	
Abnormal dreams or nightmares	5 (1%)	18 (5%)	
Insomnia	5 (1%)	10 (3%)	
Nausea	3 (1%)	8 (2%)	
Rash (rash, macular/maculopapular/papular/pustular/scaly rash, erythema, allergic dermatitis, urticaria, drug eruption, exanthem, toxic skin eruption, urticaria papular)	6 (2%)	26 (8%)	0.0002
Treatment-emergent grade 3 or 4 laboratory abnormalities in ≥2% of pts in either gp	N=345	N=340	
Any grade 3 or 4 laboratory abnormality	34 (10%)	55 (16%)	
Increased pancreatic amylase	11 (3%)	16 (5%)	
Increased aspartate aminotransferase	8 (2%)	12/339 (4%)	
Hypophosphataemia	6 (2%)	4/339 (1%)	
Increased alanine aminotransferase	4 (1%)	12 (4%)	
Increased LDL-C	3 (1%)	8/339 (2%)	
Increased triglycerides	1 (0%)	5/339 (2%)	
Increased total cholesterol	1 (0%)	6/339 (2%)	
Mean (95% CI) change in total cholesterol (mmol/L)	0.03 (-0.06 to 0.11)	0.63 (0.53 to 0.73)	<0.0001
Mean (95% CI) change in HDL-C (mmol/L)	0.07 (0.04 to 0.10)	0.24 (0.21 to 0.27)	<0.0001
Mean (95% CI) change in total cholesterol/HDL-C	-0.14 (-0.33 to 0.05)	-0.24 (-0.40 to -0.09)	0.25
Mean (95% CI) change in LDL-C (mmol/L)	-0.04 (-0.10 to 0.03)	0.31 (0.23-0.39)	<0.0001
Mean (95% CI) change in triglycerides (mmol/L)	-0.10 (-0.19 to -0.01)	0.16 (-0.07 to 0.38)	0.01
Grade 3 rash Grade 4 rash	1 0	2 0	
Grade 3 or 4 abnormalities in creatinine	0	0	
Discontinuation for renal adverse events	0	0	
Mean change from baseline in QT interval corrected according to Fridericia's formula	10.9 ms (9.0-12.8)	12.0 ms (10.1-13.7)	

Authors' conclusion

These data suggest that once-daily rilpivirine, perhaps as a single tablet regimen in combination with tenofovir-disoproxil fumarate and emtricitabine, is expected to be a valuable treatment option for patients infected with HIV who have not been previously treated with antiretroviral drugs.

Reference	Study type/ quality	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
Cohen, C. J., J. Andrade-Villanueva, et al. (2011). "Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial." Lancet **378**(9787):	**RCT: NCT00543725; TMC278 against HIV, in a once-daily regimen versus efavirenz (THRIVE)** **Allocation to treatment** Random Method of randomisation: computer generated interactive web-response system Concealment: adequate **Blinding** double blinded **Sample size calculation** yes **ITT analysis** Yes **Setting:** Outpatients	**Total N: 680**	**INCLUSION CRITERIA** adults (≥18 years) naive to antiretroviral therapy, with a screening plasma viral load of ≥5000 copies/mL and viral sensitivity to the background N(t)RTIs, as assessed with the vircoTYPE HIV-1 assay **EXCLUSION CRITERIA** HIV-2 infection, presence of at least one of 39 NNRTI resistance-associated mutations (RAMs) active clinically significant disease (e.g. pancreatitis, cardiac dysfunction, active and significant psychiatric disorder, adrenal insufficiency, or hepatic impairment), renal impairment, pregnancy or breastfeeding. Disallowed drugs were all investigational drugs, drugs that could reduce rilpivirine exposure (e.g. those with a potent cytochrome 3A4-inducing effect or proton-pump inhibitors), drugs disallowed for efavirenz or the background regimen (as per the package inserts) and any anti-HIV therapy other than those used in the trial.	**Drug(s):** rilpivirine (TMC278) 25mg once daily + N(t)RTI regimen, which included tenofovir-disoproxil-fumarate plus emtricitabine (60%), zidovudine plus lamivudine (30%), or abacavir plus lamivudine (10%).	**Drug(s):** efavirenz 600mg once daily + N(t)RTI regimen, which included tenofovir-disoproxil-fumarate plus emtricitabine (60%), zidovudine plus lamivudine (30%), or abacavir plus lamivudine (10%). **n=340 (2 not treated)**	**Treatment duration:** 96 weeks **Assessments at:** wks 2, 4, 8, 12 and 16, and every 8 wks thereafter. **Follow-up after end of treatment:** 4 weeks	**Primary endpoint:** non-inferiority of rilpivirine to efavirenz in terms of % of all pts who received at least one dose of rilpivirine or efavirenz who had a confirmed virological response (defined by the intent-to-treat TLOVR algorithm) at 48 wks with a non-inferiority margin of 12%. Other endpoints: non-inferiority with a 10% margin and superiority (if non-inferiority was shown), antiviral activity in time, changes from baseline in CD4 cell count, safety, tolerability, HIV genotypic and phenotypic characteristics (in virological failures), adherence (assessed by the Modified Medication Adherence	**Tibotec**

229-237.			**Baseline comparability between groups**: **Age**: median (range) 36 (19‑62) years on rilpivirine and 36 (19‑69) on efavirenz **Gender**: 90 (26%) female on rilpivirine and 94 (28%) on efavirenz **Severity of disease:** median (range) CD4 cell count 263 (2‑744) cells/ml on rilpivirine and 263 (1‑1137) on efavirenz	**n=340**			Self-Report Inventory), pharmacokinetics, and pharmacokinetic and pharmacodynamic relations	

Main outcomes:

	Rilpivirine N=340	**Efavirenz N=338**	**difference (95% CI)**
Patients who received at least one drug dose			
Viral load <50 copies per mL	291 (86%)	276 (82%)	3.9% (‑1.6 to 9.5)
Virological failure (efficacy endpoint) Rebounders (confirmed response before wk 48 with confirmed rebound ≤week 48) Never suppressed (no confirmed response before week 48)	24 (7%) 8 (2%) 16 (5%)	18 (5%) 7 (2%) 11 (3%)	
Discontinuation due to adverse event or death	9 (3%)	24 (7%)	
Other discontinuation (lost to follow-up, non-compliance, withdrew consent, ineligible to continue, or sponsor's decision)	16 (5%)	20 (6%)	
Predicted response (%) Primary analysis adjusted for baseline viral load and background nucleoside or nucleotide reverse transcriptase inhibitors.	87%	83%	3.5% (‑1.7 to 8.8)
Per-protocol population Viral load <50 copies per mL	287/334 (86%)	273/332 (82%)	3.7% (‑1.9 to 9.3)

Other outcomes:
At wk 48, the mean change from baseline in CD4 cell count was 189 cells per µL (95% CI 174‑203) with rilpivirine and 171 cells per µL (155‑187) with efavirenz (p=0.09).

	Rilpivirine N=340	Efavirenz N=338
Virological failure (resistance analysis): any pt who received at least one dose of drug who had a treatment failure irrespective of time of failure, treatment status, or reason for discontinuation, providing the following criteria were met: never achieved two consecutive viral load values of <50 copies per mL and had an increase in viral load of 0·5 log10 copies per mL or more above the nadir (never suppressed) or first achieved two consecutive viral load values of < 50 copies per mL followed by two consecutive (or single, when last available) viral load values ≥50 copies per mL (rebounder)	27 (8%)	20 (6%)
Virological failure (resistance analysis) with resistance data at time of failure: With any treatment-emergent NNRTI and/or IAS–USA N(t)RTI RAM	15/22 (68%)	8/15 (53%)
NNRTI RAM incidence in patients who failed with NNRTI mutations		
E138K	10/13 (77%)	0/7
K101E	3/13 (23%)	1/7 (14%)
V189I	2/13 (15%)	0/7
H221Y	2/13 (15%)	0/7
K103N	0/13	4/7 (57%)
V106M	0/13	2/7 (29%)
Y188C	0/13	2/7 (29%)
IAS–USA N(t)RTI RAM incidence in patients who failed with N(t)RTI mutations		
M184I and/or V	12/14 (86%)	3/5 (60%)
M184V only	5/14 (36%)	3/5 (60%)
M184I only	4/14 (29%)	0/5
M184I/V mixtures	3/14 (21%)	0/5
K65R	0	2/5 (40%)

48 weeks	Rilpivirine N=340	Efavirenz N=344	p value
Median treatment duration (weeks; range)	55 (2‑83)	55 (0‑84)	
Any adverse event	313 (92%)	312 (92%)	
Any treatment-related adverse event of grade 2 or greater	54 (16%)	104 (31%)	<0.0001
Adverse event leading to permanent discontinuation	15 (4%)	25 (7%)	
Any serious adverse event (including death)	22 (7%)	24 (7%)	
Death	1 (<1%)	3 (1%)	
Most common treatment-related adverse event of grade 2 or greater in ≥2% of pts in			

either group (excluding laboratory abnormalities reported as an adverse event) Insomnia Headache Nausea Dizziness Rash (rash, macular/maculopapular/papular/pustular/scaly rash, erythema, allergic dermatitis, urticaria, drug eruption, exanthem, toxic skin eruption, urticaria papular)	 7 (2%) 5 (1%) 2 (1%) 0 1 (<1%)	 6 (2%) 9 (3%) 9 (3%) 20 (6%) 30 (9%)	 <0.0001
Treatment-emergent grade 3 or 4 laboratory abnormalities in ≥2% of pts in either gp Any grade 3 or 4 laboratory abnormality Increased pancreatic amylase Increased aspartate aminotransferase Increased alanine aminotransferase Reduced white blood cell count Increased LDL-C Increased triglycerides Increased total cholesterol Increased lipase (fasting)	 41/340 (12%) 9/340 (3%) 6/340 (2%) 6/340 (2%) 7/340 (2%) 2/340 (1%) 1/340 (<1%) 0/340 2/340 (1%)	 63/330 (19%) 11/330 (3%) 7/330 (2%) 11/330 (3%) 5/329 (2%) 19/327 (6%) 10/329 (3%) 11/329 (3%) 5/330 (2%)	
Mean (95% CI) change in total cholesterol (mmol/L)	0.08 (‑0.01 to 0.16)	0.79 (0.69 to 0.90)	<0.0001
Mean (95% CI) change in HDL-C (mmol/L)	0.11 (0.08 to 0.13)	0.27(0.24 to 0.30)	<0.0001
Mean (95% CI) change in total cholesterol/HDL-C	‑0.36 (‑0.48 to ‑0.25)	‑0.28 (‑0.38 to ‑0.17)	0. 25
Mean (95% CI) change in LDL-C (mmol/L)	‑0.02 (‑0.09 to 0.05)	0.44 (0.34 to 0.53)	<0.0001
Mean (95% CI) change in triglycerides (mmol/L)	‑0.07 (‑0.17 to 0. 04)	0.14 (0.01 to 0.26)	<0.0001
Grade 3 rash Grade 4 rash	0 0	1/338 0	
Grade 3 or 4 abnormalities in creatinine	0	0	
Discontinuation for renal adverse events	0	0	
Mean change from baseline in QT interval corrected according to Fridericia's formula	12.0 ms (10.1‑13.8)	14.1 ms (12.3‑16.0)	

Authors' conclusion

Rilpivirine is expected to be a valuable treatment option for antiretroviral-naive patients infected with HIV-1.

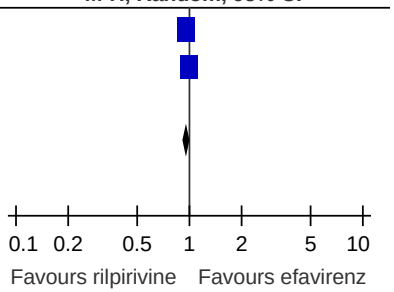
Forest plots for Rilpivirine versus efavirenz:

Viral suppression <50 copies/mL.

	Efavirenz		Rilpirivine			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Cohen 2011 (THRIVE)	276	338	291	340	50.8%	0.95 [0.89, 1.02]	
Molina 2011 (ECHO)	285	344	287	346	49.2%	1.00 [0.93, 1.07]	
Total (95% CI)		**682**		**686**	**100.0%**	**0.98 [0.93, 1.02]**	
Total events	561		578				

Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.34); I² = 0%

Test for overall effect: Z = 1.01 (P = 0.31)

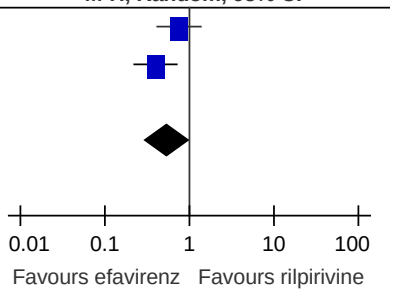


Virological failure.

	Efavirenz		Rilpirivine			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Cohen 2011 (THRIVE)	18	338	24	340	49.5%	0.75 [0.42, 1.36]	
Molina 2011 (ECHO)	15	344	38	346	50.5%	0.40 [0.22, 0.71]	
Total (95% CI)		**682**		**686**	**100.0%**	**0.55 [0.29, 1.02]**	
Total events	33		62				

Heterogeneity: Tau² = 0.12; Chi² = 2.31, df = 1 (P = 0.13); I² = 57%

Test for overall effect: Z = 1.89 (P = 0.06)

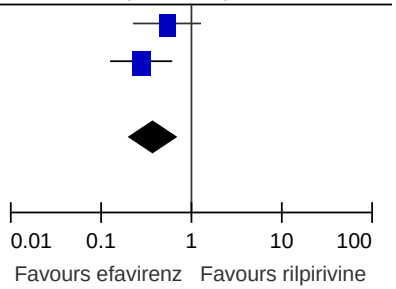


Drug resistance.

Study or Subgroup	Efavirenz Events	Total	Rilpirivine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cohen 2011 (THRIVE)	8	338	15	340	46.3%	0.54 [0.23, 1.25]
Molina 2011 (ECHO)	8	344	29	346	53.7%	0.28 [0.13, 0.60]
Total (95% CI)		**682**		**686**	**100.0%**	**0.38 [0.20, 0.72]**
Total events	16		44			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 1.29$, df = 1 (P = 0.26); $I^2 = 22\%$

Test for overall effect: Z = 2.96 (P = 0.003)

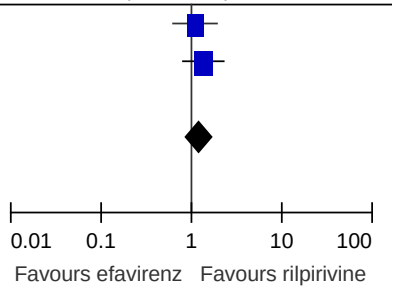


Serious adverse event.

Study or Subgroup	Efavirenz Events	Total	Rilpirivine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cohen 2011 (THRIVE)	24	338	22	340	46.3%	1.10 [0.63, 1.92]
Molina 2011 (ECHO)	31	344	23	346	53.7%	1.36 [0.81, 2.28]
Total (95% CI)		**682**		**686**	**100.0%**	**1.23 [0.84, 1.80]**
Total events	55		45			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.30$, df = 1 (P = 0.59); $I^2 = 0\%$

Test for overall effect: Z = 1.07 (P = 0.29)

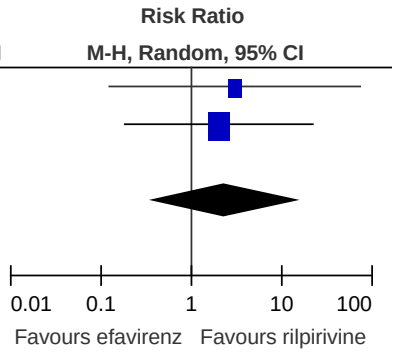


Grade 3 or 4 rash.

Study or Subgroup	Efavirenz Events	Efavirenz Total	Rilpirivine Events	Rilpirivine Total	Weight	Risk Ratio M-H, Random, 95% CI
Cohen 2011 (THRIVE)	1	338	0	340	36.0%	3.02 [0.12, 73.82]
Molina 2011 (ECHO)	2	344	1	346	64.0%	2.01 [0.18, 22.08]
Total (95% CI)		**682**		**686**	**100.0%**	**2.33 [0.34, 15.83]**
Total events	3		1			

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%

Test for overall effect: Z = 0.86 (P = 0.39)

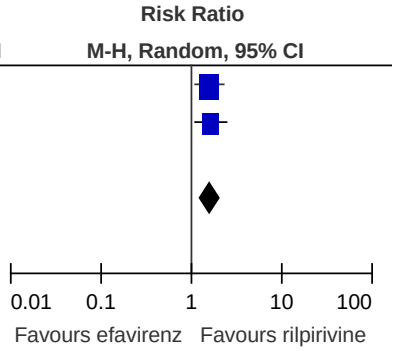


Grade 3 or 4 laboratory adverse event.

Study or Subgroup	Efavirenz Events	Efavirenz Total	Rilpirivine Events	Rilpirivine Total	Weight	Risk Ratio M-H, Random, 95% CI
Cohen 2011 (THRIVE)	63	330	41	340	54.9%	1.58 [1.10, 2.28]
Molina 2011 (ECHO)	55	340	34	345	45.1%	1.64 [1.10, 2.45]
Total (95% CI)		**670**		**685**	**100.0%**	**1.61 [1.23, 2.11]**
Total events	118		75			

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.90); I² = 0%

Test for overall effect: Z = 3.47 (P = 0.0005)

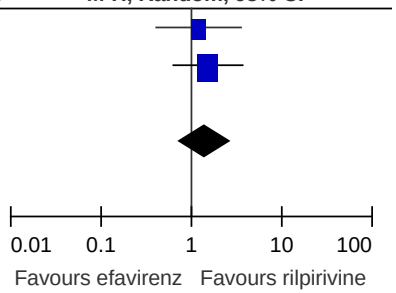


Grade 3 or 4 AST.

Study or Subgroup	Efavirenz Events	Efavirenz Total	Rilpirivine Events	Rilpirivine Total	Weight	Risk Ratio M-H, Random, 95% CI
Cohen 2011 (THRIVE)	7	330	6	340	40.0%	1.20 [0.41, 3.54]
Molina 2011 (ECHO)	12	339	8	345	60.0%	1.53 [0.63, 3.69]
Total (95% CI)		**669**		**685**	**100.0%**	**1.39 [0.70, 2.75]**
Total events	19		14			

Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%

Test for overall effect: Z = 0.94 (P = 0.35)

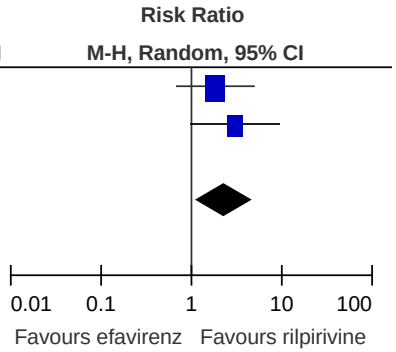


Grade 3 or 4 ALT.

Study or Subgroup	Efavirenz Events	Efavirenz Total	Rilpirivine Events	Rilpirivine Total	Weight	Risk Ratio M-H, Random, 95% CI
Cohen 2011 (THRIVE)	11	338	6	340	56.5%	1.84 [0.69, 4.93]
Molina 2011 (ECHO)	12	340	4	345	43.5%	3.04 [0.99, 9.34]
Total (95% CI)		**678**		**685**	**100.0%**	**2.29 [1.09, 4.80]**
Total events	23		10			

Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 1 (P = 0.51); I² = 0%

Test for overall effect: Z = 2.20 (P = 0.03)

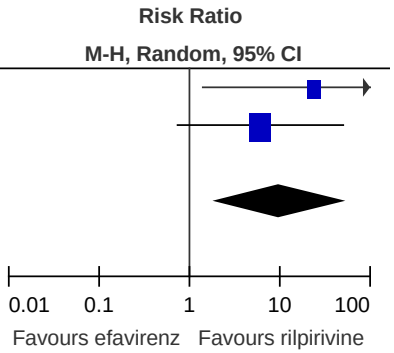


Grade 3 or 4 total cholesterol.

Study or Subgroup	Efavirenz Events	Efavirenz Total	Rilpirivine Events	Rilpirivine Total	Weight	Risk Ratio M-H, Random, 95% CI
Cohen 2011 (THRIVE)	11	329	0	340	35.8%	23.77 [1.41, 401.68]
Molina 2011 (ECHO)	6	339	1	345	64.2%	6.11 [0.74, 50.45]
Total (95% CI)		**668**		**685**	**100.0%**	**9.93 [1.83, 53.94]**
Total events	17		1			

Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%

Test for overall effect: Z = 2.66 (P = 0.008)

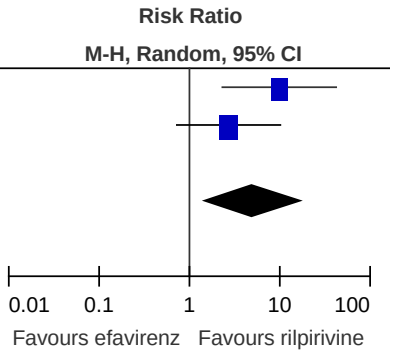


Grade 3 or 4 LDL cholesterol.

Study or Subgroup	Efavirenz Events	Efavirenz Total	Rilpirivine Events	Rilpirivine Total	Weight	Risk Ratio M-H, Random, 95% CI
Cohen 2011 (THRIVE)	19	327	2	340	47.3%	9.88 [2.32, 42.07]
Molina 2011 (ECHO)	8	339	3	345	52.7%	2.71 [0.73, 10.14]
Total (95% CI)		**666**		**685**	**100.0%**	**5.00 [1.38, 18.17]**
Total events	27		5			

Heterogeneity: Tau² = 0.37; Chi² = 1.74, df = 1 (P = 0.19); I² = 43%

Test for overall effect: Z = 2.44 (P = 0.01)

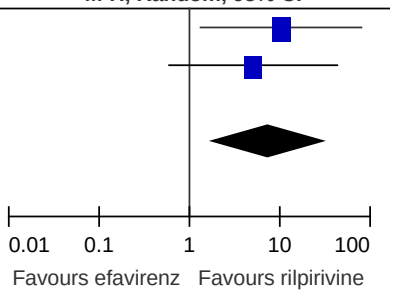


Grade 3 or 4 triglycerides.

	Efavirenz		Rilpirivine			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Cohen 2011 (THRIVE)	10	329	1	340	52.2%	10.33 [1.33, 80.28]	
Molina 2011 (ECHO)	5	339	1	345	47.8%	5.09 [0.60, 43.33]	
Total (95% CI)		**668**		**685**	**100.0%**	**7.36 [1.67, 32.39]**	
Total events	15		2				

Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%

Test for overall effect: Z = 2.64 (P = 0.008)

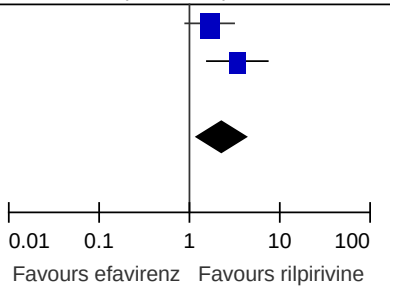


Discontinuation due to adverse event.

	Efavirenz		Rilpirivine			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Cohen 2011 (THRIVE)	25	338	15	340	55.5%	1.68 [0.90, 3.12]	
Molina 2011 (ECHO)	27	344	8	346	44.5%	3.39 [1.56, 7.37]	
Total (95% CI)		**682**		**686**	**100.0%**	**2.29 [1.15, 4.57]**	
Total events	52		23				

Heterogeneity: Tau² = 0.12; Chi² = 1.95, df = 1 (P = 0.16); I² = 49%

Test for overall effect: Z = 2.36 (P = 0.02)



NNT/NNH table for rilpivirine versus efavirenz

Efavirenz and rilpivirine were **equally *effective*** (outcomes of viral suppression, virological failure).

The only significant differences between the drugs were for the following *safety* outcomes:

	Efavirenz better	Rilpivirine better	ARR	NNT
Drug resistance	yes	no	40/1000	25
Grade 3 or 4 laboratory adverse event	no	yes	67/1000	
Grade 3 or 4 ALT	no	yes	19/1000	
Grade 3/4 total cholesterol	no	yes	13/1000	
Grade 3/4 LDL cholesterol	no	yes	29/1000	
Grade 3 or 4 triglycerides	no	yes	19/1000	
Discontinuation due to adverse event	no	yes	43/1000	

25 people would need to be treated with efavirenz rather than rilpivirine to avoid 1 case of drug resistance. But this is at the expense of more laboratory adverse events and discontinuations due to adverse events.

If 1000 people were treated with efavirenz rather than rilpivirine, there would be 40 fewer cases of drug resistance, but 67 more grade 3 or 4 laboratory adverse events and 43 more discontinuations due to adverse events.

C Raltegravir versus efavirenz

Two randomised trials were found comparing raltegravir versus efavirnez:

- STARTMRK
  - Lennox, J. L., E. DeJesus, et al. (2009). "Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial." Lancet**374**(9692): 796-806.
  - Lennox, J. L., E. Dejesus, et al. (2010). "Raltegravir versus Efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses." Journal of Acquired Immune Deficiency Syndromes: JAIDS**55**(1): 39-48.
- Protocol 004
  - Markowitz, M., B.-Y. Nguyen, et al. (2009). "Sustained antiretroviral effect of raltegravir after 96 weeks of combination therapy in treatment-naive patients with HIV-1 infection." Journal of Acquired Immune Deficiency Syndromes: JAIDS**52**(3): 350-356

Reference	Study type/ quality	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
Lennox, J. L., E. DeJesus, et al. (2009). "Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial." Lancet **374** (9692): 796-806.	**RCT:** STARTMRK (MK-0518 Protocol 021) **Allocation to treatment** Random Method of randomisation: central interactive voice response system according to a computer-generated	**Total N: 563** 36 pts (13%) in the raltegravir gp and 50 pts (18%) in the efavirenz gp discontinued the	**INCLUSION CRITERIA** treatment-naive HIV-infected patients ≥18 years of age with vRNA levels >5000 copies/mL without genotypic resistance to tenofovir, emtricitabine, and/or efavirenz **EXCLUSION CRITERIA** renal insufficiency or acute or decompensated chronic hepatitis or any medical disorder that could possibly affect the undertaking or interpretation of the study **Baseline comparability**	**Drug(s):** raltegravir 400mg + coformulated tenofovir and emtricitabine (Truvada) **n=281**	**Drug(s):** efavirenz 600mg + coformulated tenofovir and emtricitabine (Truvada) **n=282**	**Treatment duration:** 96 weeks **Assessments at:** 48 and 96 weeks; clinical status was assessed at regularly scheduled visits	**Primary endpoint:** noninferior antiretroviral activity determined by the proportion of pts achieving vRNA levels <50 copies/mL at 48 wks Other endpoints: vRNA levels <50 copies/mL at 96 weeks, changes from baseline CD4 cell counts, pre-specified subgroup analyses based on	Merck and Co, Inc

Lennox, J. L., E. Dejesus, et al. (2010). "Raltegravir versus Efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses." JAIDS **55**(1): 39-48.	randomized allocation schedule Concealment: adequate **Blinding** double blinded **Sample size calculation** yes **ITT analysis** Yes **Setting:** Outpatients	study before week 96.	**between groups**: yes **Age**: median (range) 37 (19–67) on raltegravir and 36 (19–71) years on efavirenz **Gender**: 227 (81%) male on raltegravir and 231 (82%) on efavirenz **Severity of disease:** median (range) CD4 cell count 212 (1–620) cells/ml on raltegravir and 204 (4–807) on efavirenz			and as needed **Follow-up after end of treatment:** none	demographic and prognostic factors at baseline, time to virologic response, time to loss of virologic response, adverse events, lipid levels, glucose levels and body composition measurements by DEXA	

Main outcomes:

	%* Patients (95% CI) With HIV RNA <50 copies/mL		**Change‡ From Baseline CD4 cells/mm^3 (95% CI)**	
	48-Week	**96-Week**	**48-Week**	**96-Week**
Raltegravir	241/280; 86% (82 to 90)	81% (76 to 86), n=281 [228]	189 (174 to 204), n=280	240 (220 to 259), n=281
Efavirenz	230/281; 82% (77 to 86)	79% (74 to 83), n=282 [223]	163 (148 to 178), n=281	225 (206 to 244), n=282
Difference between treatment groups	4.2 (-1.9 to 10.3), p for non-inferiority <0.001	2 (-4 to 9), p for non-inferiority <0.001	26 (4 to 47), p=0.0184	15 (-13 to 42)

*Missing data were handled by counting non-completers as failures

‡Missing data were handled by the observed-failure approach with baseline values carried forward for virologic failures.

Resistance: Week 96	**Raltegravir (n=281)**	**Efavirenz (n=282)**
Virological failure	39	45
Had both vRNA levels >400 copies/ mL and available genotyping results	16/39	11/45
Resistant viruses	Raltegravir-resistant virus: 4/12 pts in the raltegravir group in which the integrase gene was amplified (1 case each showing Q148H + G140S, Q148R + G140S, Y143H + L74L/M + E92Q + T97A, Y143R); in the 3 cases	The reverse transcriptase gene could not be amplified in 2/11 pts in the efavirenz arm. 5/9 evaluable patients had efavirenz-resistant virus (1 case each showing K103N, K103N + V108I, K103K/N

	with data on the reverse transcriptase gene, the viruses were sensitive to tenofovir and resistant to emtricitabine. In the 4 remaining cases where the integrase gene could not be amplified, there were 2 patients who developed resistance to emtricitabine.	+ V106V/M, K103N, K103N + V108I + P225H); the efavirenz resistant virus was emtricitabine resistant but sensitive to tenofovir in 2 cases and susceptible to both emtricitabine and tenofovir in the other 3 cases.

Other outcomes:
Time to confirmed virologic response was significantly shorter for raltegravir recipients than efavirenz recipients (P < 0.001). Time to loss of confirmed virologic response did not significantly differ by treatment arm (P = 0.276).

Adverse events

	Clinical Adverse Events				Laboratory Adverse Events			
48 weeks	Raltegravir N=281 n (%)	Efavirenz N=282 n (%)	Difference Δ (95% CI)	p	Raltegravir N=281 n (%)	Efavirenz N=282 n (%)	Difference Δ (95% CI)	p
With ≥ 1 AE	253 (90.0%)	272 (96.5%)	–6.4% (–10.9 to –2.4)	0.002	27 (9.6%)	41 (14.5%)	–4.9% (–10.4 to 0.5)	0.092
With drug-related AE[§]	124 (44.1%)	217 (77.0%)	–32.8% (–40.2 to –25.0)	<0.0001	14 (5.0%)	24 (8.5%)	–3.5% (–7.9 to 0.7)	0.130
With serious AE	28 (10.0%)	27 (9.6%)	0.4% (–4.6 to 5.4)	0.888	0	1 (0.4%)	–0.4% (–2.0 to 1.0)	1.000
With serious drug-related AE[§]	4 (1.4%)	5 (1.8%)	–0.4% (–2.8 to 2.1)	1.000	0	0	0.0% (–1.4 to 1.4)	ND
Discontinued study medications due to AE	9 (3.2%)	17 (6.0%)	–2.8% (–6.6 to 0.7)	0.159	0	1 (0.4%)	–0.4% (–2.0 to 1.0)	1.000
Discontinued due to drug-related AE[§]	3 (1.1%)	11 (3.9%)	–2.8% (–5.9 to –0.3)	ND	0	1 (0.4%)	–0.4% (–2.0 to 1.0)	ND
Discontinued due to serious AE	7 (2.5%)	4 (1.4%)	1.1% (–1.4 to 3.8)	ND	0	0	0.0% (–1.4 to 1.4)	ND
Discontinued due to serious drug-related AE[§]	1 (0.4%)	2 (0.7%)	–0.4% (–2.2 to 1.3)	ND	0	0	0.0% (–1.4 to 1.4)	ND

	Clinical Adverse Events				Laboratory Adverse Events			
96 weeks	Raltegravir N=281 n (%)	Efavirenz N=282 n (%)	Difference Δ (95% CI)	p	Raltegravir N=281 n (%)	Efavirenz N=282 n (%)	Difference Δ (95% CI)	p
With ≥ 1 AE	266 (95)	275 (98)	-3 (-6 to 0.4)	0.086	36 (13)	59 (21)	-8 (-14 to -1.9)	0.013
With drug-related AE[§]	132 (47)	220 (78)	-31 (-38 to -23)	<0.001	19 (7)	35 (12)	-6 (-11 to -1)	0.031
With serious AE	40 (14)	34 (12)	2 (-4 to 8)	0.457	0 (0)	2 (1)	-1 (-3 to 1)	0.499
With serious drug-related AE[§]	6 (2)	5 (2)	0.4 (-2 to 3)	0.772	0 (0)	12 (0.4)	-0.4 (-2 to 1)	1.000
Discontinued study medications due to AE	11 (4)	17 (6)	-2 (-6 to 2)	0.333	0 (0)	3 (1)	-1 (-3 to 0.3)	0.249
Discontinued due to drug-related AE[§]	3 (1)	12 (4)	-3 (-6 to -1)	ND	0 (0)	2 (7)	-0.7 (-3 to 0.7)	ND
Discontinued due to serious AE	9 (3)	5 (2)	1 (-1 to 4)	ND	0 (0)	1 (0.4)	-0.4 (-2 to 1)	ND
Discontinued due to serious drug-related AE[§]	1 (0.4)	2 (0.7)	-0.4 (-2.2 to 1.3)	ND	0 (0)	1 (0.4)	-0.4 (-2 to 1)	ND
Nervous system side effects Depression Depression SAE	29% 21 (8%) 2	61% 25 (9%) 2	-32% (-39 to -24)	<0.001				

[§]Determined by investigator to be possibly, probably, or definitely drug-related to any drug in the study regimen.
ND = not done (because the test was not prespecified in the data analysis plan).

96 weeks	Raltegravir N=281 n (%)	Efavirenz N=282 n (%)
Serious musculoskeletal AE	1 (myopathy)	0
Immune reconstitution syndromes as AE	19 (7%)	13 (5%)
New or recurrent cancers	3 (1%): Kaposi sarcoma, basal cell carcinoma, and metastatic lung cancer	11 (4%): Kaposi sarcoma (6); basal cell carcinoma (2); bone cancer, B-cell lymphoma, squamous cell carcinoma of the anus (1 each)
Death (not drug-related)	3: Kaposi sarcoma, cerebral haemorrhage, and metastatic lung cancer	0
Death (drug-related)	0	0

Most common specific drug-related (determined by investigator to be possibly, probably, or definitely related to any drug in the study regimen) clinical adverse events of moderate to severe intensity present in ≥2% of either treatment group:

	Raltegravir N=281 n (%)		Efavirenz N=282 n (%)	
	Week 48	**Week 96**	**Week 48**	**Week 96**
Rash: includes the MedDRA terms for unspecified, generalized, macular, and/or papular rashes (but not for allergic dermatitis, drug eruption, eczema, and skin lesion) under the category of ''Skin and Subcutaneous Tissue Disorders''		0 (0.0)		19 (6.7)
Headache	11 (4%)	11 (3.9)	13 (5%)	13 (4.6)
Dizziness	4 (1%)	4 (1.4)	18 (6%)	18 (6.4)
Insomnia	10 (4%)	10 (3.6)	9 (3%)	9 (3.2)
Nausea	8 (3%)	8 (2.8)	10 (4%)	10 (3.5)
Fatigue	4 (1%)	5 (1.8)	8 (3%)	8 (2.8)
Diarrhoea	3 (1%)	3 (1.1)	8 (3%)	8 (2.8)

Grade 3/4* Laboratory Abnormalities

	Raltegravir N=281 n (%)		Efavirenz N=282 n (%)	
	Week 48	**Week 96**	**Week 48**	**Week 96**
Absolute neutrophil count <750 cells/mL	5 (2%)	7/281 (2.5)	3 (1%)	3/278 (1.1)
Haemoglobin <7.5 gm/dL	2 (1%)	2/281 (0.7)	2 (1%)	2/278 (0.7)
Platelet count <50,000/mL		0/276 (0.0)		1/276 (0.4)
Fasting total cholesterol >300 mg/dL		0/276 (0.0)		11/267 (4.1)
Fasting LDL-cholesterol ≥190 mg/dL	3 (1%)	3/271 (1.1)	10/280 (4%)	17/262 (6.5)
Fasting triglycerides >750 mg/dL	1 (<1%)	1/276 (0.4)	3 (1%)	4/267 (1.5)
Fasting glucose >250 mg/dL		3/274 (1.1)		0/266 (0.0)
Total bilirubin >2.5 x ULN		2/281 (0.7)		0/279 (.0)
Alkaline phosphatase >5 x ULN		0/281 (0.0)		2/279 (0.7)
Aspartate aminotransferase >5 x ULN	6 (2%)	9/281 (3.2)	5 (2%)	8/279 (2.9)
Alanine aminotransferase >5 x ULN	5 (2%)	5/281 (1.8)	6 (2%)	7/279 (2.5)

Lipoatrophy (loss of ≥20% appendicular fat)		3/37 (8%)		2/38 (5%)

	Raltegravir N=281 n (%)	Efavirenz N=282 n (%)	p value	Raltegravir N=281 n (%)	Efavirenz N=282 n (%)	p value
	Week 48: mean (SD)			**Week 96:** mean (no SDs given)		
Mean change (mg/dL) in total cholesterol	0·55 (1·62)	1·82 (1·87)	<0·0001	10	38	≤0.001
Mean change (mg/dL) in HDL cholesterol	0·23 (0·47)	0·56 (0·61)	<0·0001	3	10	≤0.001
Mean change (mg/dL) in LDL cholesterol	0·33 (1·37)	0·89 (1·61)	0·0002	7	21	≤0.001
Mean change (mg/dL) in triglycerides	–0·16 (4·52)	2·08 (7·16)	<0·0001	-4	40	≤0.00
Mean change in the total cholesterol:HDL-cholesterol ratio	–0·02 (0·06)	–0·01 (0·08)	0·2924	-0.18	0.04	0.192
Mean change (mg/dL) from baseline glucose levels				2	6	0.025

Authors' conclusion
Raltegravir had noninferior antiretroviral efficacy relative to efavirenz through 96 weeks of therapy. Although raltegravir was associated with significantly fewer drug-related clinical adverse events of any intensity than efavirenz, the rates of serious clinical adverse events and discontinuations due to clinical adverse events were similar in each treatment arm. Metabolic perturbations were modest in both treatment groups. Raltegravir provides another potent and durable therapeutic option for the initial treatment of HIV-1–infected patients.

Reference	Study type/ quality	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Funding
Markowitz, M., B.-Y. Nguyen, et al. (2009). "Sustained antiretroviral effect of raltegravir after 96 weeks of combination	**RCT: Protocol 004** **Allocation to treatment** Random Method of randomisation: not stated Concealment: not stated **Blinding**	**Total N: 185**	**INCLUSION CRITERIA** treatment-naive HIV-1–infected pts with plasma HIV-1 RNA levels ≥5000 copies/mL and CD4+ T-cell counts ≥100 cells /mm^3 at screening. Part I consisted of 10 days of raltegravir monotherapy in 35 pts. Part II examined the safety, tolerability, and efficacy of raltegravir dosed 100, 200, 400, or 600 mg twice daily vs efavirenz	**Drug(s):** raltegravir 100, 200, 400 or 600mg twice daily + tenofovir 300mg and lamivudine 300mg daily. It was previously reported that	**Drug(s):** efavirenz 600 mg per day + tenofovir 300mg per day and lamivudine	**Treatment duration:** 96 weeks **Assessments at:** wks 60, 72, 84 and 96	**Primary endpoint:** proportion of pts achieving plasma HIV-1 RNA <400 copies/ml Other endpoints: proportion of pts achieving plasma HIV-1 RNA <50	Merck & Co

therapy in treatment-naive patients with HIV-1 infection." JAIDS **52**(3): 350-356	double blinded **Sample size calculation** This was an estimation study only and was not powered for formal efficacy comparisons between raltegravir and efavirenz. **ITT analysis** Yes **Setting:** Outpatients		600 mg per day, each with tenofovir 300 mg per day and lamivudine 300 mg per day, for up to 48 weeks in 30 pts from part I (cohort I) plus 171 pts randomized into part II (cohort II). Ps who reached week 48 of the original study were given the option to continue in a double-blind extension. Pts who received any dose of raltegravir in the original study received raltegravir 400 mg twice a day in the extension phase. Pts who received efavirenz in the original study continued on efavirenz in the extension. Both open-label drugs, tenofovir and lamivudine, continued unchanged in the extension. **EXCLUSION CRITERIA** not stated **Baseline comparability between groups**: yes **Age**, g**ender**: not stated **Severity of disease:** mean CD4 cell count ranged between the groups from 271 to 338 cells/ml	all doses of raltegravir showed generally similar efficacy and safety at wk 48 in this study; after wk 48, all pts on raltegravir received 400 mg bd so the efficacy data beyond week 48 are displayed in this current analysis as a single raltegravir gp that combines all original dose gps. **n=150; 148 entered extension phase**	300mg per day **n=35; all entered extension phase**	**Follow-up after end of treatment:** none	copies/mL change from baseline in HIV-1 RNA (log10 copies/mL), and the change from baseline in CD4+ T-cell count.	
Main outcomes:								
			Raltegravir 400 mg twice a day (N =	**Efavirenz 600 mg every day (N = 38)**			Difference (95% CI)	

	160) n (%)		**n (%)**		
	n/N	% (95% CI)	n/N	% (95% CI)	
HIV-1 RNA <400 copies/mL:					
Week 48	148/160	92.5 (87.3 to 96.1)	33/38	86.8 (71.9 to 95.6)	5.7 (-3.4 to 20.3)
Week 96	135/160	84.4 (77.8 to 89.6)	32/38	84.2 (68.7 to 94.0)	0.2 (-10.6 to 15.6)
HIV-1 RNA <50 copies/mL					
Week 48	137/160	85.6 (79.2 to 90.7)	33/38	86.8 (71.9 to 95.6)	-1.2 (-11.2 to 13.7)
Week 96	133/160	83.1 (76.4 to 88.6)	32/38	84.2 (68.7 to 94.0)	-1.1 (-12.0 to 14.5)
	Mean (95% CI) change from baseline		Mean (95% CI) change from baseline		
Mean change from baseline in HIV-1 RNA					
Week 48	-2.32 (-2.43 to -2.22)		-2.29 (-2.55 to -2.03)		-0.03 (-0.31 to 0.24)
Week 96	-2.30 (-2.42 to -2.19)		-2.28 (-2.57 to -2.00)		-0.02 (-0.33 to 0.29)
Change from baseline in CD4+ T-cell count					
Week 48	174 (153 to 196)		170 (125 to 215)		4 (-45 to 54)
Week 96	221 (197 to 246)		232 (180 to 285)		-11 (-69 to 47)
Virological failure/resistance					
Week 96	6/160: 3 had resistance-associated mutations in both the integrase and reverse transcriptase coding regions. The integrase mutations were N155H; L74L/M, V151I, N155H; and Y143C, S230R in the 3 pts. One additional pt who failed raltegravir developed a mutation only in the reverse transcriptase region. 2 pts had no resistance-associated mutations in either the integrase or reverse transcriptase coding regions		2/38: Both patients in whom efavirenz-based therapy failed had mutations conferring resistance to both nucleoside reverse transcriptase inhibitor and nonnucleoside reverse transcriptase inhibitor elements of their regimen.		

Other outcomes:

Week 96	**Raltegravir 400 mg twice a day (N = 160) n (%)**	**Efavirenz 600 mg every day (N = 38) n (%)**
One or more clinical adverse events	146 (91.3)	35 (92.1)

Serious clinical adverse events	16 (10.0)	3 (7.9)
Discontinued due to clinical adverse event	2 (1.3)	1 (2.6)
Drug-related* clinical adverse events†	82 (51.3)	28 (73.7)
Diarrhoea	11 (6.9)	4 (10.5)
Nausea	20 (12.5)	5 (13.2)
Vomiting	4 (2.5)	3 (7.9)
Flatulence	9 (5.6)	1 (2.6)
Dizziness	14 (8.8)	11 (28.9)
Headache	14 (8.8)	9 (23.7)
Abnormal dreams	10 (6.3)	7 (18.4)
Insomnia	13 (8.1)	4 (10.5)
Nightmares	0 (0.0)	4 (10.5)
Fatigue	8 (5.0)	2 (5.3)
Malaise	2 (1.3)	3 (7.9)
Anxiety	2 (1.3)	2 (5.3)
Lethargy	2 (1.3)	2 (5.3)
Disturbance in attention	1 (0.6)	2 (5.3)
One or more laboratory adverse events	38 (23.8)	11 (28.9)
Discontinued due to laboratory adverse event	1 (0.6)	0 (0.0)
Drug-related* laboratory adverse events†	19 (11.9)	3 (7.9)
Aspartate aminotransferase increased	7 (4.4)	2 (5.3)
Alanine aminotransferase increased	6 (3.8)	2 (5.3)

*Determined by investigator to be possibly, probably, or definitely related to any drug in the study regimen.

† Specific events occurring in at least 5% of patients in 1 or more treatment groups

Grade 3/4† Abnormalities for Prespecified Laboratory Tests

Week 96	**Raltegravir 400 mg twice a day (N = 160) n (%)**	**Efavirenz 600 mg every day (N = 38) n (%)**
Absolute neutrophil count <750 cells/mL	1 (0.6)	0 (0.0)
Haemoglobin <7.5 gm/dL	0	0
Platelet count <50,000/mL	0	0
Fasting total cholesterol >300 mg/dL	0 (0.0)	2 (5.3)
Fasting LDL-cholesterol ≥190 mg/dL	1 (0.6)	2 (5.3)

Fasting triglycerides >750 mg/dL	0 (0.0)	3 (7.9)
Fasting glucose >250 mg/dL	0	0
Total bilirubin >2.5 x ULN	0	0
Alkaline phosphatase >5 x ULN	1 (0.6)	0 (0.0)
Aspartate aminotransferase >5 x ULN	4 (2.5)	1 (2.6)
Alanine aminotransferase >5 x ULN	2 (1.3)	2 (5.3)
Creatinine	0	0
Pancreatic amylase >2 x ULN	4 (2.5)	0 (0.0)
Lipase >3 x ULN	2 (1.3)	0 (0.0)
Creatine kinase ≥10 x ULN	10 (6.3)	1 (2.6)

	Raltegravir N=160 n (%)	Efavirenz N=38 n (%)	p value
Mean change (mg/dL) in total cholesterol			
Week 48	-2.3	+20.7	<0.001
Week 96	+1.1	+24.0	0.002
Mean change (mg/dL) in HDL cholesterol			
Week 48	+4.8	+9.8	0.010
Week 96	+7.4	+13.0	0.017
Mean change (mg/dL) in LDL cholesterol			
Week 48	-7.5	+3.0	0.016
Week 96	-5.8	+4.4	0.045
Mean change (mg/dL) in triglycerides			
Week 48	-1.0	+49.5	0.068
Week 96	-10.8	+13.4	0.145
Mean change in the total cholesterol:HDL-cholesterol ratio			
Week 48	-0.6	-0.5	0.530
Week 96	-0.7	-0.7	0.689

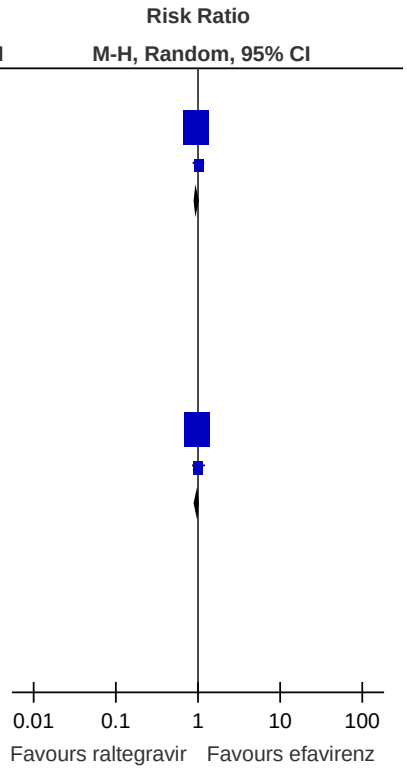
Authors' conclusion

Raltegravir 400 mg twice daily in combination with 2 nucleoside reverse transcriptase inhibitors has demonstrated potent durable efficacy similar to that of an efavirenz-based regimen and has been generally well tolerated.

Forest plots for raltegravir versus efavirenz

Viral suppression <50 copies/mL.

Study or Subgroup	Efavirenz Events	Efavirenz Total	Raltegravir Events	Raltegravir Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 48 weeks						
Lennox 2009 (STARTMRKw48)	230	281	241	280	78.7%	0.95 [0.88, 1.02]
Markowitz 2009 (004)	33	38	137	160	21.3%	1.01 [0.88, 1.17]
Subtotal (95% CI)		**319**		**440**	**100.0%**	**0.96 [0.90, 1.03]**
Total events	263		378			
Heterogeneity: Tau² = 0.00; Chi² = 0.65, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 1.11 (P = 0.27)						
3.1.2 96 weeks						
Lennox 2010 (STARTMRKw96)	223	282	228	281	77.8%	0.97 [0.90, 1.06]
Markowitz 2009 (004)	32	38	133	160	22.2%	1.01 [0.87, 1.18]
Subtotal (95% CI)		**320**		**441**	**100.0%**	**0.98 [0.91, 1.06]**
Total events	255		361			
Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.46 (P = 0.64)						

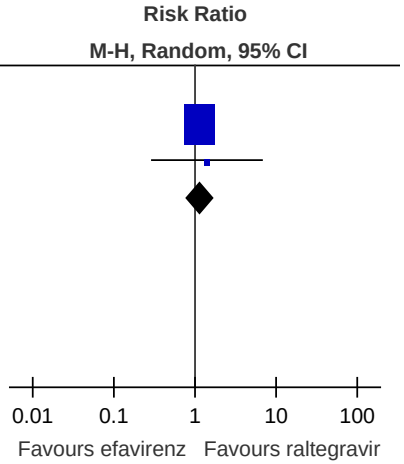


Virological failure.

Study or Subgroup	Efavirenz Events	Total	Raltegravir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.2 96 weeks						
Lennox 2010 (STARTMRKw96)	45	282	39	281	94.0%	1.15 [0.77, 1.71]
Markowitz 2009 (004)	2	38	6	160	6.0%	1.40 [0.29, 6.68]
Subtotal (95% CI)		**320**		**441**	**100.0%**	**1.16 [0.79, 1.71]**
Total events	47		45			

Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%

Test for overall effect: Z = 0.77 (P = 0.44)

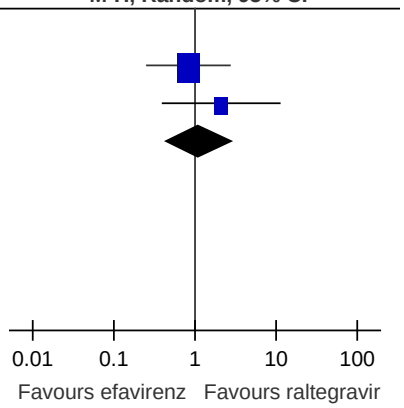


Drug resistance.

Study or Subgroup	Efavirenz Events	Efavirenz Total	Raltegravir Events	Raltegravir Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.2 96 weeks						
Lennox 2010 (STARTMRKw96)	5	282	6	281	66.6%	0.83 [0.26, 2.69]
Markowitz 2009 (004)	2	38	4	160	33.4%	2.11 [0.40, 11.07]
Subtotal (95% CI)		**320**		**441**	**100.0%**	**1.13 [0.43, 2.96]**
Total events	7		10			

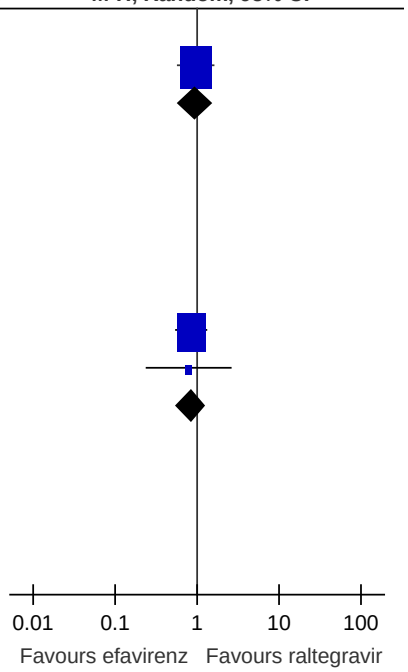
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 1 (P = 0.37); I² = 0%

Test for overall effect: Z = 0.25 (P = 0.80)

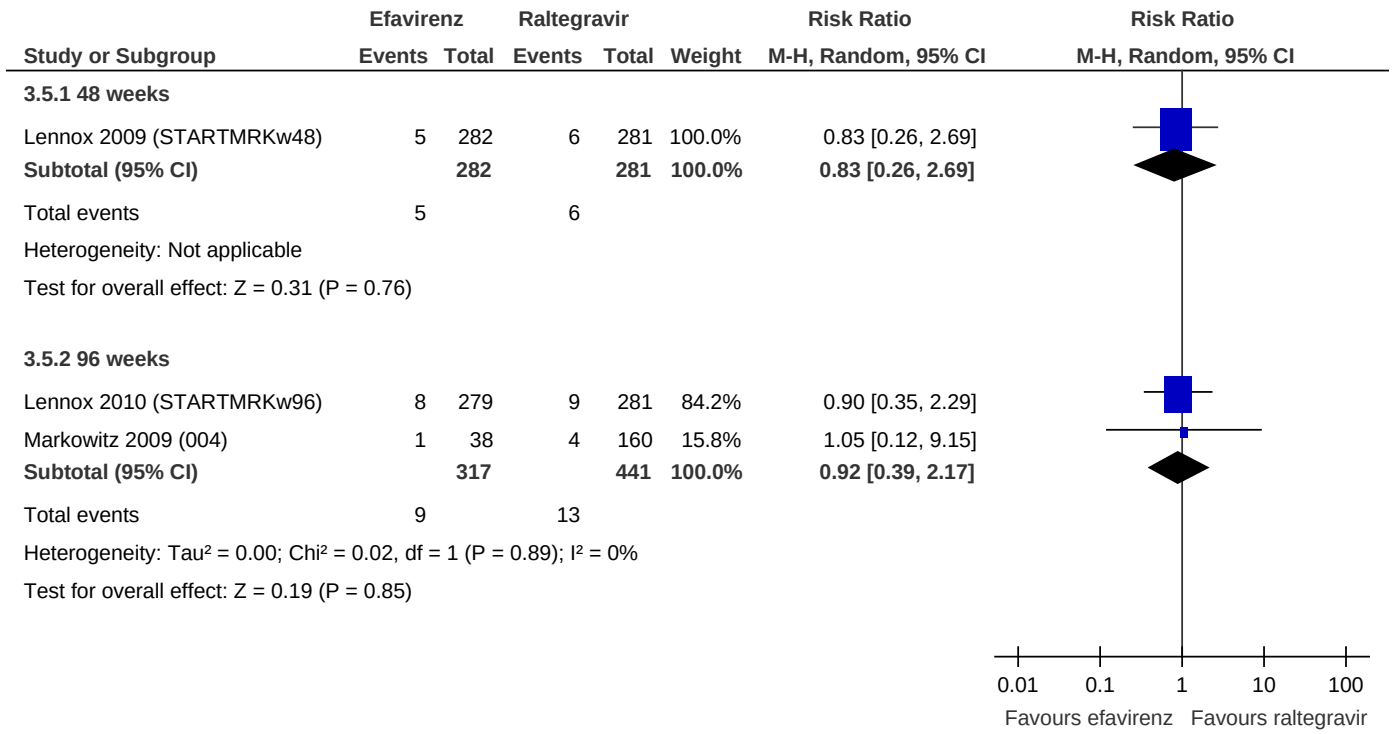


Serious adverse event.

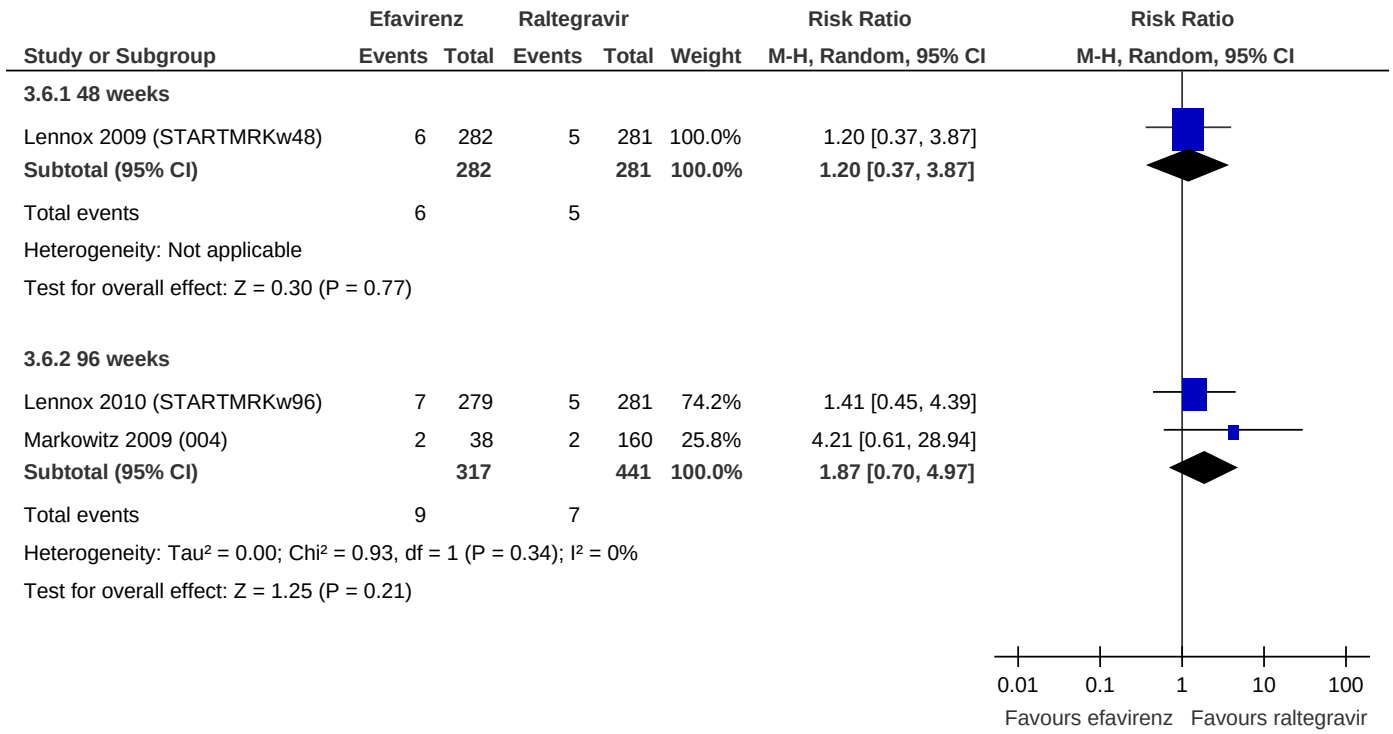
Study or Subgroup	Efavirenz Events	Efavirenz Total	Raltegravir Events	Raltegravir Total	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 48 weeks						
Lennox 2009 (STARTMRKw48)	27	282	28	281	100.0%	0.96 [0.58, 1.59]
Subtotal (95% CI)		**282**		**281**	**100.0%**	**0.96 [0.58, 1.59]**
Total events	27		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.88)						
3.4.2 96 weeks						
Lennox 2010 (STARTMRKw96)	34	282	40	281	88.5%	0.85 [0.55, 1.30]
Markowitz 2009 (004)	3	38	16	160	11.5%	0.79 [0.24, 2.57]
Subtotal (95% CI)		**320**		**441**	**100.0%**	**0.84 [0.56, 1.25]**
Total events	37		56			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 (P = 0.91); $I^2 = 0\%$						
Test for overall effect: Z = 0.85 (P = 0.39)						



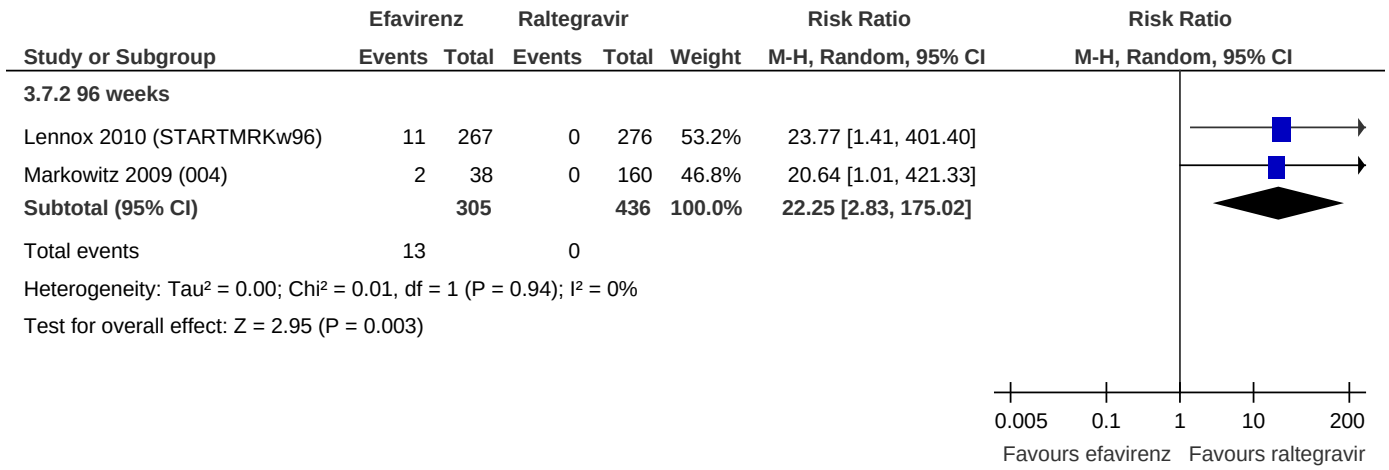
Grade 3 or 4 AST elevation.



Grade 3 or 4 ALT elevation.

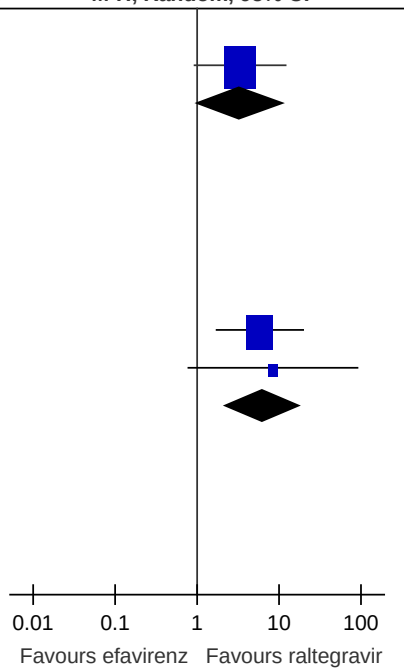


Grade 3 or 4 total cholesterol.



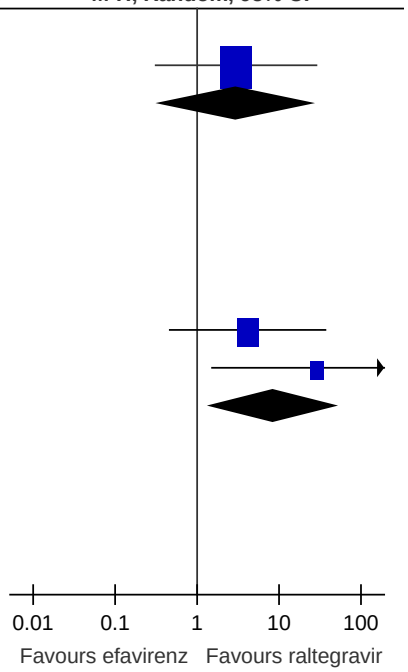
Grade 3 or 4 LDL cholesterol.

Study or Subgroup	Efavirenz Events	Efavirenz Total	Raltegravir Events	Raltegravir Total	Weight	Risk Ratio M-H, Random, 95% CI
3.8.1 48 weeks						
Lennox 2009 (STARTMRKw48)	10	280	3	281	100.0%	3.35 [0.93, 12.03]
Subtotal (95% CI)		**280**		**281**	**100.0%**	**3.35 [0.93, 12.03]**
Total events	10		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.85 (P = 0.06)						
3.8.2 96 weeks						
Lennox 2010 (STARTMRKw96)	17	263	3	271	79.2%	5.84 [1.73, 19.69]
Markowitz 2009 (004)	2	38	1	160	20.8%	8.42 [0.78, 90.47]
Subtotal (95% CI)		**301**		**431**	**100.0%**	**6.30 [2.14, 18.59]**
Total events	19		4			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.07$, df = 1 (P = 0.78); $I^2 = 0\%$						
Test for overall effect: Z = 3.33 (P = 0.0009)						



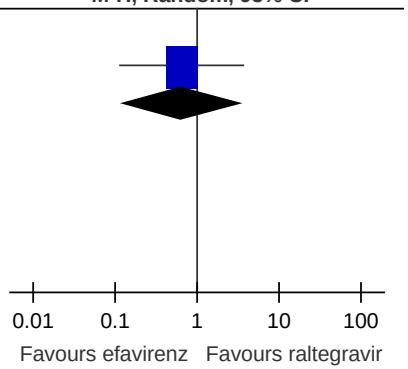
Grade 3 or 4 triglycerides.

Study or Subgroup	Efavirenz Events	Efavirenz Total	Raltegravir Events	Raltegravir Total	Weight	Risk Ratio M-H, Random, 95% CI
3.9.1 48 weeks						
Lennox 2009 (STARTMRKw48)	3	282	1	281	100.0%	2.99 [0.31, 28.57]
Subtotal (95% CI)		**282**		**281**	**100.0%**	**2.99 [0.31, 28.57]**
Total events	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.95 (P = 0.34)						
3.9.2 96 weeks						
Lennox 2010 (STARTMRKw96)	4	267	1	276	63.4%	4.13 [0.47, 36.76]
Markowitz 2009 (004)	3	38	0	160	36.6%	28.90 [1.52, 547.97]
Subtotal (95% CI)		**305**		**436**	**100.0%**	**8.43 [1.34, 52.85]**
Total events	7		1			
Heterogeneity: Tau² = 0.14; Chi² = 1.08, df = 1 (P = 0.30); I² = 8%						
Test for overall effect: Z = 2.28 (P = 0.02)						



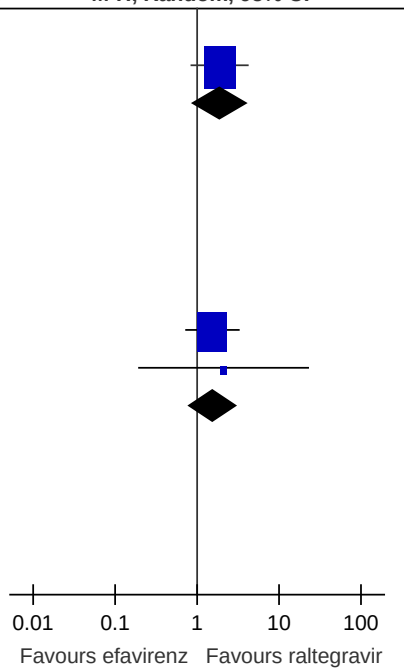
Lipoatrophy (loss of 20% or more appendicular fat).

Study or Subgroup	Efavirenz Events	Efavirenz Total	Raltegravir Events	Raltegravir Total	Weight	Risk Ratio M-H, Random, 95% CI
3.10.2 96 weeks						
Lennox 2010 (STARTMRKw96)	2	38	3	37	100.0%	0.65 [0.11, 3.67]
Subtotal (95% CI)		**38**		**37**	**100.0%**	**0.65 [0.11, 3.67]**
Total events	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.62)						



Discontinued due to adverse events.

Study or Subgroup	Efavirenz Events	Total	Raltegravir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.11.1 48 weeks						
Lennox 2009 (STARTMRKw48)	17	282	9	281	100.0%	1.88 [0.85, 4.15]
Subtotal (95% CI)		**282**		**281**	**100.0%**	**1.88 [0.85, 4.15]**
Total events	17		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.57 (P = 0.12)						
3.11.2 96 weeks						
Lennox 2010 (STARTMRKw96)	17	282	11	281	91.1%	1.54 [0.73, 3.23]
Markowitz 2009 (004)	1	38	2	160	8.9%	2.11 [0.20, 22.62]
Subtotal (95% CI)		**320**		**441**	**100.0%**	**1.58 [0.78, 3.21]**
Total events	18		13			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.06$, df = 1 (P = 0.81); $I^2 = 0\%$						
Test for overall effect: Z = 1.27 (P = 0.20)						



NNT/NNH table for raltegravir versus efavirenz

Efavirenz and raltegravir were **equally *effective*** (outcomes of viral suppression, virological failure).

The only significant differences between the drugs were for the following *safety* outcomes:

	Efavirenz better	raltegravir better	ARR	NNT
Grade 3/4 total cholesterol	no	yes	cannot be calculated as raltegravir had no events	cannot be calculated as raltegravir had no events
Grade 3/4 LDL cholesterol	no	yes	49/1000	20
Grade 3 or 4 triglycerides	no	yes	17/1000	

20 people would need to be treated with raltegravir rather than efavirenz to avoid 1 case of Grade 3/4 LDL cholesterol

D Darunavir versus efavirenz

No randomised trials were found comparing darunavir versus efavirenz directly, so an indirect comparison was suggested using a) darunavir versus lopinavir/r and b) lopinavir/r versus efavirenz. This indirect comparison is only valid if there is little heterogeneity between the studies included in the two parts of the comparison.

a) darunavir versus lopinavir/r

One randomised trial was found comparing darunavir versus lopinavir/r:

- ARTEMIS
    - Ortiz, R., E. Dejesus, et al. (2008). "Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48."AIDS**22**(12): 1389-1397.
    - Mills, A. M., M. Nelson, et al. (2009). "Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis." AIDS**23**(13): 1679-1688.
    - Nelson, M., P.-M. Girard, et al. (2010). "Suboptimal adherence to darunavir/ritonavir has minimal effect on efficacy compared with lopinavir/ritonavir in treatment-naive, HIV-infected patients: 96 week ARTEMIS data." Journal of Antimicrobial Chemotherapy**65**(7): 1505-1509.

b) lopinavir/r versus efavirenz

Three randomised trials were found comparing lopinavir/r versus efavirenz:

- LAKE
    - Echeverria, P., E. Negredo, et al. (2010). "Similar antiviral efficacy and tolerability between efavirenz and lopinavir/ritonavir, administered with abacavir/lamivudine (Kivexa), in antiretroviral-naive patients: a 48-week, multicentre, randomized study (Lake Study)." Antiviral Research**85**(2): 403-408.
- NCT00162643
    - Sierra-Madero, J., A. Villasis-Keever, et al. (2010). "Prospective, randomized, open label trial of Efavirenzvs Lopinavir/Ritonavir in HIV+ treatment-naive subjects with CD4+<200 cell/mm3 in Mexico." Journal of Acquired Immune Deficiency Syndromes: JAIDS**53**(5): 582-588
- ACTG5142:

- Riddler SA NEJM 2008, 358(20): 2095-106
- Stein, J. H., L. Komarow, et al. (2008). "Lipoprotein changes in HIV-infected antiretroviral-naive individuals after starting antiretroviral therapy: ACTG Study A5152s." Journal of Clinical Lipidology **2**(6): 464-471.

Examples of factors that might cause heterogeneity of comparative treatment effects

A. Different quality or methods of randomized trials	i. Adequate concealment of randomisation ii. Blinding iii. Duration of follow-up iv. Loss to follow-up v. Cross-over
B. Confounding factors in relation to participant populations	i. Age ii. Sex iii. Genetic variation iv. Diagnostic workup v. Intensity of surveillance vi. Severity of pathology vii. Physiological reserve viii. Stage or duration of disease ix. Prior therapy x. Co-existing disease xi. Background therapy of concomitant treatments/advances in standard of care
C. Confounding factors in relation to circumstances	i. Health systems ii. Geography iii. Setting in hospital or ambulatory care iv. Date of trials
D. Different treatment (common reference and interventions)	i. Dose ii. Duration iii. Timing
E. Different outcome measures and methods of statistical analysis	i. Definition ii. Rating instrument iii. Frequency of measurement iv. Start point of measurement against duration or progression of disease or treatment, especially in time-to-event analyses

Reference	Ortiz 2008, Mills 2009, Nelson 2010	Echeverria 2010	Sierra-Madero 2010	Riddler 2008, Stein 2008	Comparability?
Name of study	**ARTEMIS**	**LAKE**	**MEXICO**	**ACTG 5142**	-
A. Different quality or methods of randomized trials					
i. Adequate concealment of randomisation	yes	not stated	yes	not stated	Probably OK
ii. Blinding	no – open label	no	no	no	OK
iii. Duration of follow-up	192 weeks of treatment	48 weeks of treatment	48 weeks of treatment	median follow-up was 112 weeks	Large variation from 48-192 weeks
iv. Loss to follow-up a) did not receive therapy; b) withdrawals (including insufficient efficacy, toxicity, adverse events, death) c) lost	total: 17% darunavir and 23% lopinavir; a) 3/343 pts (1%) + 0/346 pts; b) 41/343 (11%) + 70/346 (20%); c) 18/343 (5%) + 11/346 (3%)	a) none; b) 16/63 (25%) efavirenz and 9/63 (14%) lopinavir; c) 2/63 (3%) efavirenz and 14/63 (22%) lopinavir	a) none; b)12/95 (13%) efavirenz and 28/94 (30%) lopinavir; c) 15/95 (16%) efavirenz and 11/94 (12%) lopinavir	a) none; b) 118/573 (21%): 19 died, 56 unable to attend clinic visits, 26 unwilling to adhere to the protocol, 17 other reasons; c) 46/573 (8%) could not be contacted	All studies should be viewed with caution because of the large (>20%) numbers of losses/ dropouts
v. Cross-over	none	none	none	none	OK
B. Confounding factors in relation to participant populations					
i. Age	mean 35.5 years on darunavir and 35.3 on lopinavir	mean 39 (±8.45) years efavirenz and 37(±9.41) lopinavir	median (IQR) 35 (29, 42) years	median 38 years	OK
ii. Sex	239/343 (70%) male on darunavir and 241/346 (70%) on lopinavir	86% male on efavirenz and 86.8% on lopinavir	161/189 (85%) male	80% male	OK
iii. Genetic variation	Black 80 (23%) darunavir and 71 (21%) lopinavir; Caucasian 137 (40%) and 153 (44%); Hispanic 77 (22%) and 77 (22%); Oriental/Asian 44 (13%) and 38 (11%); Other 4 (1%) and 5 (1%);	Race not stated	Race not stated	White 274 (36%); Black 314 (42%); Hispanic 146 (19%); Asian 15 (2%); Other or unknown 4 (1%)	unclear if comparable or not

Reference	Ortiz 2008, Mills 2009, Nelson 2010	Echeverria 2010	Sierra-Madero 2010	Riddler 2008, Stein 2008	Comparability?
	Missing 1 (1%) and 2 (1%)				
iv. Diagnostic workup	tested for clinical or laboratory evidence of significantly decreased hepatic function or decompensation; grade 3 or 4 laboratory abnormalities	HLAB* 5701 test was not determined at baseline (genetic test was not easily available at that time).	opportunistic infection excluded or treated	Genotyping for resistance to HIV-1 drugs was performed during screening	Difference diagnostic procedures prior to studies
v. Intensity of surveillance	Assessments at 2 wks, then every 4 wks until wk 16, at wk 24, and every 12 wks until wk 192	wk 4 and every 3 mo thereafter until wk 48	entry and at wks 4, 8, 16, 24, 32, and 48	entry, and at wks 1, 4, 8, 12, 16, 20, and 24 and every 8 wks thereafter	varied from 4-12 weeks
vi. Stage or duration of disease	Mean (SD) duration of infection 2.4 (3.6) years on darunavir and 2.5 (3.6) on lopinavir; median CD4 cell count 225cells/ml	Median time from HIV diagnosis: 20.9±57.9 months; mean CD4 cell count 193 (±122) cells/ml on efavirenz and 191 (±127) on lopinavir	CD4+ count <200/mm3 required as inclusion criterion: median (IQR) CD4 cell count 56 (25, 117) cells/ml	median CD4 cell count 191cells/ml	Patients in Sierra-Madero 2010 had a much lower CD4+ cell count at baseline representing much more severe disease; exclude in sensitivity analysis
vii. Prior therapy	none	none	none	none	OK
viii. Activities score	not assessed	not assessed	not assessed	not assessed	OK
ix. Background therapy of concomitant treatments/advances in standard of care	tenofovir 300mg qd and emtricitabine 200mg qd	abacavir (600mg)/ lamivudine (300mg) (Kivexa®) once daily	zidovudine/lamivudine 300/150 mg bid	NRTIs: lamivudine (Epivir) for all pts (150 mg bd or 300mg once daily) plus the choice of 1 of 3 other agents: zidovudine (Retrovir) 300mg twice daily, stavudine extended release (XR) (Zerit XR) 100mg once daily (with pts weighing <60kg receiving 75mg), or tenofovir disoproxil fumarate (DF) (Viread)	unclear if it is OK to assume that all these backbones can be treated as identical

Reference	Ortiz 2008, Mills 2009, Nelson 2010	Echeverria 2010	Sierra-Madero 2010	Riddler 2008, Stein 2008	Comparability?
				300mg once daily. The choice of the 2nd NRTI was made by the site investigator before randomization; changes in NRTI were not allowed during the study	
C. Confounding factors in relation to circumstances					
i. Geography	26 countries (including North, Central and South America, Europe, Australia, Malaysia, Singapore, South Africa, Taiwan, Thailand)	19 centres in Spain (18) and Italy (1)	10 clinical sites in 5 states of Mexico	USA	Unclear if these are sufficiently similar
ii. Setting in hospital or ambulatory care	Outpatients	Outpatients	Outpatients	Outpatients	OK
;iii. Date of trials: a) Enrollment dates; b) Cutoff date for outcomes	a) from 28 September 2005 (end date not stated) b) 13 June 2007 for 48 week analysis; 8 May 2008 for 96 week analysis	a) March 2005 to March 2006 b) not stated	a) January 2005 to January 2007; b) not stated	a) January 2003 to May 2004; b) not stated	ACTG 5142 recruited earlier than the other studies – unclear if the difference is important
D. Different treatment (common reference and interventions)					
Treatment Arm 1	**LOPINAVIR/RITONAVIR**	**LOPINAVIR/ RITONAVIR**	**LOPINAVIR/ RITONAVIR**	**LOPINAVIR/ RITONAVIR**	lopinavir arms
i. Dose	800/200mg total daily dose	lopinavir (400mg, 3 capsules)/ritonavir (100mg) twice daily	400/ 100 mg [three 133/ 33.3 mg capsules (fixed-dose, soft-gel formulation) bid]	400 mg lopinavir and 100 mg of ritonavir (Kaletra capsules) bd	OK
ii. Duration	192 weeks	48 weeks	48 weeks	112 weeks	Large variation from 48-192 weeks
iii. Timing	400/100mg bid or 800/200mg daily	400/100mg bid	twice daily	twice daily	
Treatment Arm 2	**DARUNAVIR/ RITONAVIR**	**EFAVIRENZ**	**EFAVIRENZ**	**EFAVIRENZ**	Efavirenz arms
i. Dose	800/100mg daily	600 mg daily	600 mg daily	600mg daily	OK
ii. Duration	192 weeks	48 weeks	48 weeks	112 weeks	Large variation from 48-112 weeks
iii. Timing	daily	daily	daily	daily	OK

Reference	Study type/ quality	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
Ortiz R, E Dejesus et al. (2008). "Efficacy and safety of once-daily darunavir/ ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48." AIDS **22**(12): 1389-1397. Mills, A. M., M. Nelson, et al. (2009). "Once-daily darunavir/ ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis." AIDS **23**(13): 1679-1688.	**RCT: ARTEMIS (AntiRetroviral Therapy with TMC114 ExaMined In naive Subjects)** **Allocation to treatment** Random Method of randomisation: central randomization system (interactive voice response) Concealment: adequate **Blinding** not blinded (open label) **Sample size calculation** yes	**Total N: 689**	**INCLUSION CRITERIA** treatment-naive HIV-1-infected pts aged at least 18 years, with plasma HIV-1 RNA at least 5000 copies/ml **EXCLUSION CRITERIA** active AIDS-defining illness; any clinically significant disease; clinical or laboratory evidence of significantly decreased hepatic function or decompensation; acute viral hepatitis at screening or calculated creatinine clearance <70 ml/min; primary HIV infection or pregnant or breastfeeding. Pts with grade 3 or 4 laboratory abnormalities were not eligible with some exceptions (diabetes or asymptomatic glucose, triglyceride or cholesterol elevations) unless clinical assessment identified health risks. Pts coinfected with chronic hepatitis B or C were allowed entry if their condition was clinically stable and they did not require treatment during the study period.	**Drug(s):** DRV/r 800/100mg qd + tenofovir 300mg qd and emtricitabine 200mg qd **ITT n=343; PP n=340**	**Drug(s):** lopinavir/ritonavir (LPV/r) 800/200mg total daily dose (400/100mg bid or 800/200mg qd depending on local regulator approval and investigator or pt prefer	**Treatment duration:** 192 weeks **Assessments at:** 2 wks, then every 4 wks until wk 16, at wk 24, and every 12 wks until wk 192	**Primary endpoint:** non-inferiority of DRV/r 800/100 mg qd as compared with LPV/r 800/200 mg total daily dose in virologic response (a confirmed plasma HIV-1 RNA <50 copies/ml by per-protocol time-to-loss of virologic response (PP-TLOVR) at 48 weeks. Other endpoints: other virologic and immunologic parameters over 192 weeks (including proportion of pts with HIV-1 RNA <400 copies/ ml, change in HIV-1 RNA and CD4 cell count change from baseline); evaluation of safety and tolerability; and in the event of non-inferiority, testing for superiority of DRV/r over LPV/r (planned analysis). Nelson 2010: Self-reported treatment adherence measured using the Modified Medication Adherence Self-Report Inventory (M-MASRI) questionnaire at wks 4, 12, 24, 36, 48, 60, 72, 84 and 96. The validity of these adherence measurements was assessed by correlation with self-reported	Gilead donated Truvada; Tibotec BVBA supported drafting the manuscript

Nelson M, P-M Girard et al. (2010). "Suboptimal adherence to darunavir/ritonavir has minimal effect on efficacy compared with lopinavir/ ritonavir in treatment-naive, HIV-infected patients: 96 week ARTEMIS data." Journal of Antimicrobial Chemotherapy **65**(7): 1505-1509.	**ITT analysis** Yes **Setting:** Outpatients; 26 countries (including North, Central and South America, Europe, Australia, Malaysia, Singapore, South Africa, Taiwan, Thailand)		**Baseline comparability between groups**: yes **Age**: mean 35.5 years on darunavir and 35.3 on lopinavir **Gender**: 239/343 (70%) male on darunavir and 241/346 (70%) on lopinavir **Race:** Black 80 (23%) darunavir and 71 (21%) lopinavir; Caucasian 137 (40%) and 153 (44%); Hispanic 77 (22%) and 77 (22%); Oriental/Asian 44 (13%) and 38 (11%); Other 4 (1%) and 5 (1%); Missing 1 (1%) and 2 (1%) **Severity of disease:** median CD4 cell count 225cells/ml **Mean (SD) duration of infection** 2.4 (3.6) years on darunavir and 2.5 (3.6) on lopinavir		ence or both) + tenofovir 300mg qd and emtricitabine 200mg qd **ITT n=346; PP n=346**	**Follow-up after end of treatment:** none	missed doses due to symptoms or side effects of HIV infection and/or antiretroviral medication for wks 4–96, and with plasma drug concentrations (wks 4–48). Pt-perceived distress caused by symptoms and side effects and their impact on adherence was assessed by a modified version of the validated Memorial Symptom Assessment Scale-Short Form (M-MSASSF) questionnaire at baseline and at wks 4, 12, 24, 48, 72 and 96. Doses of darunavir/ ritonavir or lopinavir/ ritonavir taken during the previous 30 days were calculated at each scheduled timepoint. Rates were transformed into a binary variable [adherent (>95%) and suboptimally adherent (≤95%)]. A 95% adherence level has been reported to be required to achieve optimal efficacy with protease inhibitor (PI)-based therapy.	

Main outcomes (Ortiz 2008):

Week 48	Darunavir	Lopinavir	Estimated difference between treatment responses
Wk 48 confirmed virologic response of HIV-1 RNA <50 copies/ml in the PP population	84% of 340 = 286	78% of 346 = 270	5.6% (95% CI, -0.1 to 11): the lower limit of the 95% CI was greater than -12% (P<0.001), demonstrating noninferiority of DRV/r qd as compared with LPV/r.
Median change from baseline in	137 cells/µL	141 cells/µL	

CD4 cell count (noncompleter = failure) at wk 48			
Virologic failure (HIV-1 RNA>50 copies/ml at any time before the cutoff date)	34/340 (10%)	49/346 (14%)	
Baseline and endpoint (last available timepoint during treatment) genotypes available: resistance	10: no pts developed an International AIDS Society (IAS-USA) protease inhibitor resistance-associated mutation (RAM), while one pt developed an IAS-USA nucleoside reverse transcriptase inhibitor (NRTI) RAM (M184I/V).	18: one pt developed two additional IAS-USA protease inhibitor RAMs (A71T and V77I) and 2 pts developed an IAS-USA NRTI RAM (both M184V).	

Other outcomes: Week 48

Incidence, n (%)	DRV/r (N=343)	LPV/r (N=346)	p value
Mean treatment exposure (weeks)	54.8	53.3	
≥1 adverse event	309 (90)	328 (95)	
≥1 serious adverse event	25 (7)	41 (12)	
≥1 grade 3 or 4 adverse event	64 (19)	75 (22)	
Total discontinuations	41 (12%)	56 (16%)	
≥1 adverse event leading to permanent discontinuation	12 (3)	24 (7)	p<0.05
Discontinuation due to virologic failure	2 (<1%)	6 (2%)	
Grade 2–4 adverse events at least possibly related to study treatment reported in ≥2% of pts (excluding laboratory abnormalities reported as adverse events)			
Gastrointestinal (all adverse events)	23 (7)	47 (14)	p<0.01
Diarrhoea	14 (4)	34 (10)	p<0.01
Nausea	6 (2)	10 (3)	
Rash (all types)	9 (3)	4 (1)	
Grade 2–4 laboratory abnormalities (incidence ≥2% of patients)			
Alanine aminotransferase	29 (8)	35 (10)	
Aspartate aminotransferase	32 (9)	31 (9)	

Hyperbilirubinemia Triglycerides Total cholesterol Low-density lipoprotein Hyperglycemia Pancreatic amylase Neutrophil count	2 (<1) 10 (3) 44 (13) 44 (13) 22 (6) 23 (7) 27 (8)	11 (3) 38 (11) 78 (23) 36 (10) 23 (7) 17 (5) 10 (3)	 p<0.0001 p<0.01
Serious renal adverse events	0	0	
Discontinuation due to renal event	0	0	
Death (treatment-related)	0	0	
Death (not treatment-related)	1	3	

Week 96 (Mills 2009):

	DRV/r (N=343)	LPV/r (N=346)	difference, p value
Total discontinuations n (%) AEs (including ... deaths) Lost to follow-up Withdrawal of consent Virological failure Pregnancy Noncompliance to study protocol Other	59 (17%) 13 (4%); 1 death 18 (5) 11 (3) 3 (1) 6 (2) 3 (1) 5 (1)	81 (23%) 32 (9%); 5 deaths 11 (3) 10 (3) 8 (2) 3 (1) 7 (2) 10 (3)	
Viral load of less than 50 copies/ml at week 96	79% (271)	71% (246)	8.4% (P<0.001; 95% CI 1.9–14.8) and the lower limit of the 95% CI was greater than -12% (P<0.001), demonstrating noninferiority of DRV/r q.d. relative to LPV/r.
median change from baseline in CD4 cell count [noncompleter = failure (NC=F)]	171	188	p=0.57
virologic failure	12% of 343 (41)	17% of 346 (59)	P=0.0437
Analysis of samples from patients with a viral load at least 50	n=31	n=46	

	copies/ml and paired baseline and endpoint genotypes: major (primary) protease inhibitor resistance-associated mutations one or two minor IAS-USA protease inhibitor resistance-associated mutations (almost all polymorphic); all remained susceptible to all protease inhibitors. nucleoside analogue reverse transcriptase inhibitor (NRTI) mutation (M184I or M184V) K70E mutation	 0 4 2 0	 0 7 4 1	
	≥1 serious adverse event	34 (10)	55 (16)	
	Any serious AE at least possibly related to PI	3 (1)	10 (3)	
	Any AE leading to withdrawal	19 (5.5)	35 (10.1)	
	Grade 2–4 AEs at least possibly related to study treatment (incidence ≥2% of patients) Any grade 2–4 AE Gastrointestinal AE (all) Diarrhoea Nausea Rash (all types)	 80 (23) 23 (7) 14 (4) 6 (2) 9 (3)	 119 (34) 52 (15) 38 (11) 10 (3) 5 (1)	 p<0.001
	Grade 2–4 laboratory abnormalities (incidence ≥2% of patients) Alanine aminotransferase Aspartate aminotransferase Neutrophil count Hyperglycemia Pancreatic amylase Alkaline phosphatase Partial thromboplastin time Pancreatic lipase Hyperbilirubinemia Prothrombin time Total cholesterol Calculated low-density lipoprotein Triglycerides	 38 (11) 39 (11) 30 (9) 28 (8) 25 (7) 5 (2) 8 (2) 8 (1) 4 (1) 2 (1) 60 (18) 62 (18) 15 (4)	 40 (12) 35 (10) 11 (3) 26 (8) 18 (5) 5 (2) 9 (3) 8 (2) 17 (5) 7 (2) 95 (28) 50 (15) 46 (13)	 p<0.01 p<0.001

median increases in triglycerides	0.1mmol/L (8.9mg/dL); 12%	0.6mmol/l (53.4mg/dl); 50%	p<0.001
median increases in total cholesterol	0.6mmol/L (23.4mg/dL); 15%	0.9mmol/l (35.1mg/dl); 23%	p<0.001
Serious renal adverse events	0	0	
Discontinuation due to renal event	0	0	

Nelson 2010: Mean adherence was similar between groups, ranging from 97.4% to 97.9% for darunavir/ritonavir and from 96.3% to 97.7% for lopinavir/ritonavir between weeks 4 and 96. The proportion of patients with mean adherence values >95% during the study period was high: darunavir/ritonavir 83%; lopinavir/ritonavir 78%. The proportion of adherent patients over 96 weeks ranged from 81% to 90% for darunavir/ritonavir and from 74% to 89% for lopinavir/ritonavir, and no statistically significant difference between the treatment groups was observed at any timepoint. Adherence did not vary significantly over time. In a logistical regression model including both treatment effect and adherence, virological response rates were higher in adherent compared with suboptimally adherent groups [odds ratio (OR): 2.3 (1.5–3.4)]. The difference in response rate for adherent versus suboptimally adherent patients was smaller for darunavir/ritonavir (6% difference, P=0.3312) than for lopinavir/ritonavir (25% difference, P<0.0001). Overall, the virological response rate was higher with darunavir/ritonavir versus lopinavir/ritonavir [logistical regression model, OR: 1.6 (1.09–2.3)]. In suboptimally adherent patients, a significantly higher virological response rate was seen with darunavir/ritonavir [76% (42/55)] versus lopinavir/ritonavir [53% (37/70)], P<0.01. For adherent patients, virological response rates were similar in both groups: darunavir/ritonavir 82% (221/269) and lopinavir/ritonavir 78% (196/252).

Patients with <50 copies/mL (TLOVR) at week 96 (% of those completing questionnaires)	Darunavir	Lopinavir	p value for comparison between treatment groups
Adherent (>95%)	221/269 (82%)	196/252 (78%)	NS
Sub-optimally adherent (95%)	42/55 (76%)	37/70 (53%)	p<0.01
p value for comparison between adherent and sub-optimally adherent within treatment group	0.3312	p<0.0001	

Patients reporting at least one missed dose due to symptoms were more likely to self-report suboptimal adherence (Kappa coefficients ranged from 0.16 to 0.32, P<0.001, all timepoints). Selfadherence measurements (self-reported missed doses due to symptoms weeks 4–48) were also correlated with plasma drug concentrations (weeks 4–48; P<0.01). Eleven percent (4/36) of darunavir/ritonavir patients had drug concentrations below the limit of detection (10ng/mL) at week 48 versus 14% (7/49) of lopinavir/ritonavir patients. Data for adherent patients were the same in both groups: 4% (7/199 and 7/189, respectively).

Authors' conclusion

Patients receiving once-daily DRV/r achieved high durable virologic response rates had a low rate of discontinuation due to virologic failure or adverse events or both, did not develop protease inhibitor resistance upon failure, and had suitable drug exposure. These benefits, coupled with the favorable safety and pharmacokinetic profile of DRV/r, suggest that DRV/r 800/100mg qd has the potential to become a first-line, once-daily treatment option for treatment-naive patients.

Suboptimal adherence to darunavir/ritonavir has less impact on efficacy compared with suboptimal adherence to lopinavir/ritonavir. This finding, together with darunavir's more favourable tolerability profile may help to address the adherence challenges faced by treatment-naive HIV-1-infected patients.

Reference	**Study type/ quality**	**No. pts**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Funding**
Echeverria, P, E Negredo et al. (2010). "Similar antiviral efficacy and tolerability between efavirenz and lopinavir/ ritonavir, administered with abacavir/ lamivudine (Kivexa), in antiretroviral-naive patients: a 48-week, multicentre, randomized study (Lake	**RCT: LAKE** **Allocation to treatment** Random Method of randomisation: not stated Concealment: not stated **Blinding** not blinded **Sample size calculation** yes **ITT analysis** Yes **Setting:** Outpatients; 19 centres in Spain	**Total N: 126**	**INCLUSION CRITERIA** HIV1 infected, aged 18 years or above, antitretroviral naïve, with no history of a recent opportunistic infection (<4 weeks) or immunomodulating agents before baseline. **EXCLUSION CRITERIA** **Baseline comparability between groups**: yes **Age**: mean 39 (±8.45) years efavirenz and 37(±9.41) lopinavir **Gender**: 86% male on efavirenz and 86.8% on lopinavir	**Drug(s):** efavirenz (EFV) (600 mg) + abacavir (600mg)/ lamivudine (300mg) (Kivexa®) once daily **n=63**	**Drug(s):** lopinavir (400mg, 3 capsules)/ ritonavir (100mg) twice daily plus Kivexa® once daily **n=63**	**Treatment duration:** 48 weeks **Assessments at:** wk 4 and every 3 mo thereafter until wk 48 **Follow**	**Primary endpoint:** % of responders (i.e. pts who completed 48 wks of study with the assigned treatment and maintained a viral load <50 copies/mL) Other endpoints: % of pts who experienced a virological failure; changes in CD4 cell count at week 48; changes in lipid and hepatic parameters at wk 48 from baseline, % of pts with serious (grades III and IV) adverse events; the % of	Glaxo Smith Kline Laboratories.

Study)." Antiviral Research **85**(2): 403-408.	(18) and Italy (1)		**Severity of disease:** mean CD4 cell count 193(±122) cells/ml on efavirenz and 191(±127) on lopinavir **Median time from HIV diagnosis:** 20.9±57.9 months			**-up after end of treatment:** none	pts who discontinued the study throughout 48 weeks of followup; time to treatment failure (time to virological failure or treatment discontinuation for any reason)	

Main outcomes:

48 weeks	**Efavirenz (n=63)**	**Lopinavir (n=63)**	p value
Discontinued	18	23	not stated
Lost to follow up	2	14	
Protocol deviation	1	0	
Adverse events grade I-II	10	6	
Adverse events grade III-IV	4	2	
Virological failure	1 (K103N, V179E, and M184V mutations in the transcriptase gene and the L33I mutation in the protease gene)	1 (M46L and L63P mutations in the protease gene with no mutations in the transcriptase gene)	
HIV1 RNA< 50 copies/mL at week 48 in the intention to treat analysis (Missing = Failure)	56.7% (36)	63.2% (40)	0.770

Other outcomes:

48 weeks	**Efavirenz (n=63)**	**Lopinavir (n=63)**	p value
Responders (finished study and RNA < 50 copies/mL; on treatment analysis)	87% (denominator unclear)	91.3% (denominator unclear)	0.382
Time to treatment failure	40.9±2.04 weeks	43.6±1.85 weeks	0.491
Increases in CD4 cell counts	from 193 cells/mL (±122) to 491 (±244), *P* = 0.001	from 191 cells/mL (±127) to 440 (±240), *P* = 0.002	0.126
Increase in total cholesterol	from 157±35 mg/dL to 205±28, *P* = 0.001	from 149±31 mg/dL to 193±46, *P* = 0.001	
Increase in HDL cholesterol	from 39±12 mg/dL to 49±11, *P* =	no significant increase but	

	0.001	data not shown	
Clinically evident body fat changes (moderate lipodystrophy)	0	1 (0.79%)	
Death	0	0	

Authors' conclusion

This exploratory analysis suggests similar virological effectiveness for efavirenz and lopinavir/r at 48 weeks, while slightly better immunological improvement was observed with efavirenz. The higher rate of discontinuations due to adverse events in the efavirenz group was mainly attributed to a higher incidence of hypersensitivity reaction related to the simultaneous use of abacavir and efavirenz.

Reference	Study type/ quality	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
Sierra-Madero J, A Villasis-Keever, et al. (2010). "Prospective, randomized, open label trial of Efavirenz vs Lopinavir/ Ritonavir in HIV+ treatment-naïve subjects with CD4+<200 cell/mm^3 in Mexico." JAIDS **53**(5):	**RCT: NCT00162643** **Allocation to treatment** Random Method of randomisation: using a central telephone Concealment: adequate **Blinding** not blinded **Sample size calculation** not stated **ITT analysis** Yes	**Total N: 189**	**INCLUSION CRITERIA** infected with HIV-1, aged 18 years or older, had not received previous antiretroviral treatment, and had CD4+ count <200/mm^3; required to have a plasma HIV-1 RNA level of at least 1000 copies/mL, no active opportunistic infection, a haemoglobin level >7 g/dL, a platelet count >50,000/mL, and a neutrophil count >1000/mL. Pts who had an opportunistic infection were allowed to participate after specific treatment for the infection was initiated and clinical symptoms controlled **EXCLUSION CRITERIA** active tuberculosis or any neoplasm	**Drug(s):** 600 mg of efavirenz (EFV) once daily + zidovudine / lamivudine 300/150 mg bid; changes to abacavir (300mg bid) and lamivudine (150mg bid) were allowed in cases of severe	**Drug(s):** fixed-dose lopinavir (LPV/r) 400/ 100 mg [three 133/ 33.3 mg capsules (fixed-dose, soft-gel formulation) bid] + zidovudine/ lamivudine 300/150 mg bid; changes to abacavir (300mg bid) and lamivudine (150mg bid)	**Treatment duration:** 48 wks **Assessments at:** entry and at wks 4, 8, 16, 24, 32, and 48 **Follow-up after end of**	**Primary endpoint:** proportion of pts with HIV-1 RNA <50 copies/ mL at wk 48. Other endpoints: proportion of pts with HIV-1 RNA <400 copies/mL at wk 48; change in CD4+ cell count from baseline through wk 48; adverse events, serious adverse events, discontinuations due to adverse events and grade 3 or 4 laboratory abnormalities.	National Council for Science and Technology

582-588.	**Setting:** Outpatients; 10 clinical sites in 5 states of Mexico		requiring chemotherapy **Baseline comparability between groups**: yes **Age**: median (IQR) 35 (29, 42) years **Gender**: 161/189 (85%) male **Severity of disease:** median (IQR) CD4 cell count 56 (25, 117) cells/ml	anemia or gastro-intestinal intolerance attributed to zidovudine **n=95**	were allowed in cases of severe anemia or gastro-intestinal intolerance attributed to zidovudine **n=94**	**treatment:** none		

Main outcomes:

Patient Disposition After **48 Weeks**	EFV, N = 95, n (%)	LPV/r, N = 94, n (%)	P
Completed 48 wks	68 (71)	55 (58)	0.05
HIV-RNA <50 copies/mL	67/95 (70)	50/94 (53)	0.017
Premature discontinuation: Virologic failure Lost to follow-up Adverse events Death Tuberculosis Other	 7 (7) 15 (16) 2 (2) 1 (1) 2 (2): rash, neurological toxicity	 17 (18) 11 (12) 5 (5) 2 (2) 4 (4): gastrointestinal intolerance	 0.02 0.4 0.1
No. of samples from pts who failed virologically that could be amplified for genotypic analysis (1 sample was not available and the others had a viral load below 1000 copies/ mL)	3/7: all 3 pts had resistance associated mutations (2 K103N without nucleoside mutations and 1 G190A with K65R)	5/17: 1 of 5 genotypes had a single resistance associated mutation (M184V).	

Other outcomes:

Patient Disposition After **48 Weeks**	EFV, N = 95, n (%)	LPV/r, N = 94, n (%)	P
Switched from zidovudine/lamivudine to abacavir/lamivudine because of anaemia	6	8	
Median CD4+ increase from baseline	234 cells/mm^3	239 cells/mm^3	P = 0.80

Adverse events resulting in drug discontinuation	5	11	
Serious adverse events (death, hospitalization, surgery)	17 (17.8%)	21 (22.3%)	
All grades 2–4 treatment-related AEs	68	68	
Most common grades 2–4 treatment-related AEs Gastrointestinal CNS disorders Rash Anaemia Lipids disorders LFT disorders	 11 (16.1) 24 (35)* 3 (4.4) 9 (13.2) 14 (20.5) 5 (7.3)	 15 (22) 13 (19.1)† 2 (2.9) 9 (13.2) 22 (32.3) 6 (8.8)	
Changes in total cholesterol			NS
Changes in low-density lipoprotein			NS
Changes in high-density lipoproteins			NS
Mean change in triglycerides	+48 mg/dL	+116 mg/dL	p<0.01

*20/24 AEs in the group of EFV, were attributed to the use of EFV (4 insomnia grade 2, 4 somnolence grade 2 to 4, 7 dizziness grade 2 and 3, 3 vivid dreams, and 2 headaches grade 2).

†AEs in the group of LPV/r were nonspecific and not attributed to the use of LPV/r, according to the investigators criteria (7 headaches grade 2, 2 somnolence grade 2, 2 dysaesthesias grades 2 and 3, 1 anxiety, and 1 dizziness).

Authors' conclusion

In antiretroviral therapy–naive, HIV-infected subjects presenting to care with a CD4+ count <200/mm^3, EFV-based HAART is virologically superior to LPV/r-based HAART. EFV was also virologically superior to LPV/r among patients presenting to care with CD4+ counts <100/mm^3. Further evaluation of the longterm impact of these findings is warranted. Until then, based on the information of this trial and others (ACTG 5142, Castle, Artemis) it would seem appropriate for current guidelines to recommend the use of LPV/r with caution among HIV-infected patients who present to care with very advanced disease.

Reference	**Study type/ quality**	**No. pts**	**Patient characteristics**	**Intervention**	**Comparison**	**Follow-up**	**Outcome measures**	**Funding**
Riddler SA. Class-Sparing Regimens	**RCT: ACTG5142 and AIDS Clinical Trials Group (ACTG) Study**	**Total N: 753; subst**	**INCLUSION CRITERIA** HIV-1–infected male and female pts at least 13 years of age who had not received previous antiretroviral	**Drug(s):** 600mg of efavirenz (Sustiva tablets, Bristol-Myers	**Drug(s):** a) 400 mg lopinavir and 100	**Treatment duration:** Each	**Primary endpoint:** time to virologic failure and the time to	National Institute

for Initial Treatment of HIV-1 Infection. NEJM 2008, 358(20): 2095-106. Stein JH, L Komarow et al. (2008). "Lipoprotein changes in HIV-infected antiretroviral-naive individuals after starting antiretroviral therapy: ACTG Study A5152s." Journal of Clinical Lipidology **2**(6): 464-	**A5152s (Stein substudy)** **Allocation to treatment** Random Method of randomisation: Randomization was stratified according to a permuted-block design on the basis of three factors: the screening level of plasma HIV-1 RNA (<100,000 vs. ≥ 100,000 copies/mL), the presence or absence of chronic hepatitis infection (B, C, or both), and the choice of NRTI Concealment: not stated **Blinding** not blinded **Sample size calculation** yes	**udy n=82**	therapy. All pts had a plasma HIV-1 RNA level of at least 2000 copies/mL with any CD4 cell count, and acceptable laboratory results **EXCLUSION CRITERIA** Genotyping for resistance to HIV-1 drugs was performed during screening if the site investigator suspected that the patient had been infected with HIV-1 for 1 year or less. Genotyping data were reviewed by the protocol chairs and virologist, and the patient was deemed to be ineligible for the study if any evidence of resistance to a study drug was present. Prior use of ART, known coronary artery disease, peripheral arterial disease, cerebrovascular disease, diabetes mellitus, significant kidney disease, and current use of lipid-lowering medications, insulin-sensitizing agents, antioxidant vitamin supplements, or hormones at > replacement doses. Drug treatment of diabetes mellitus and dyslipidemia were not permitted during the study **Baseline comparability between groups**: yes	Squibb) once daily plus two NRTIs (**efavirenz group; n=250**); the NRTIs used were lamivudine (Epivir, GlaxoSmithKline) for all pts (150 mg bd or 300mg once daily) plus the choice of 1 of 3 other agents: zidovudine (Retrovir, Glaxo SmithKline) 300mg twice daily, stavudine extended release (XR) (Zerit XR, investigational agent, Bristol-Myers Squibb) 100mg once daily (with pts weighing < 60kg receiving 75 mg), or tenofovir disoproxil fumarate (DF) (Viread, Gilead Sciences) 300mg	mg of ritonavir (Kaletra capsules, Abbott Laboratories) twice daily plus two NRTIs as for efavirenz group (**lopinavir-ritonavir group n=253**), **or** b) 533 mg lopinavir and 133 mg of ritonavir twice daily plus 600mg of efavirenz once daily (**NRTI-sparing group n=250**)	pt was scheduled for 96 wks of follow-up after the last enrollment; median follow-up was 112 weeks **Assessments at:** entry, and at wks 1, 4, 8, 12, 16, 20, and 24 and every 8 wks thereafter for the duration of the study **Follow-up after end of**	regimen failure among the three study groups. Virologic failure was defined as a lack of suppression of plasma HIV-1 RNA by 1 log10 or rebound before week 32 or a lack of suppression to <200 copies/mL or rebound after week 32. Confirmation of suspected virologic failure was required within 4 weeks. Regimen failure was defined as the first of either virologic failure or toxicity-related discontinuation of any component of the initial randomized treatment regimen. Other endpoints:	of Allergy and Infectious Diseases, National Institutes of Health.

471.	**ITT analysis** Yes **Setting:** Outpatients; USA		**Age**: median 38 years **Gender**: 602/753 (80%) male **Severity of disease:** median CD4 cell count 191cells/ml **Race**: white 274 (36%); Black 314 (42%); Hispanic 146 (19%); Asian 15 (2%); Other or unknown 4 (1%)	once daily. The choice of the 2nd NRTI was made by the site investigator before randomization; changes in NRTI were not allowed during the study		**treatment:** none	proportions of pts with < 200 copies/mL of plasma HIV-1 RNA; proportions of pts with <50 copies/mL of plasma HIV-1 RNA; CD4 cell count; adverse events; resistance	

Main outcomes:

589 of 753 patients (78%) completed the protocol; Of the remaining 164 patients, 19 died, 56 were unable to attend clinic visits, 26 were unwilling to adhere to the protocol, 46 could not be contacted, and 17 had other reasons. There were no significant differences among the three study groups in the reasons for loss to follow-up or the time until patients were lost to follow-up (P = 0.66).

96 weeks	**Efavirenz group; n=250**	**Lopinavir–ritonavir group n=253**	**NRTI-sparing group n=250**	Comparisons
Virologic failure	60/250 (24%)	94/253 (37%)	73/250 (29%)	Efavirenz gp had significantly longer time to virologic failure than lopinavir‑ritonavir gp (Hazard ratio 0.63 (95% CI 0.45‑0.87), P=0.006); differences between the NRTI-sparing gp and the efavirenz gp (HR 0.86 (0.61‑1.21) P=0.49) or the lopinavir‑ritonavir gp (HR 1.30 (0.95‑1.77), P=0.13) not significant.
Regimen failure	95/250 (38%)	127/253 (50%)	108/250 (43%)	There was a trend toward a longer time to regimen failure in the efavirenz gp than in the lopinavir‑ritonavir gp (HR 0.75 (95% CI 0.57‑0.98), P = 0.03), but the P value did not reach the significance level of 0.014 with adjustment for multiple comparisons. Differences between the NRTI-sparing gp and the efavirenz gp (HR 0.93, 95% CI 0.70‑1.23), and the

				Lopinavir‑ritonavir vs. NRTI-sparing therapy (HR 1.21, 95% CI 0.93‑1.56) were not significant
HIV-1 RNA <200 copies/ mL at wk 96	93% (95% CI, 88 to 96)	86% (95% CI, 80 to 91)	92% (95% CI, 87 to 96)	Efavirenz vs. lopinavir‑ritonavir P = 0.04; P>0.05 for each of the other pairwise comparisons.
HIV-1 RNA <50 copies/ mL at wk 96	89% (95% CI, 84 to 93) (223/250)	77% (95% CI, 71 to 83) (195/253)	83% (95% CI, 76 to 88)	Efavirenz vs. lopinavir‑ritonavir P = 0.003; P>0.05 for each of the other pairwise comparisons.
median increase in the CD4 cell count at wk 96	230 cells/mm^3 (IQR 142 to 353)	287 cells/ mm^3 (155 to 422)	273 cells/ mm^3 (176 to 419)	Changes greater in lopinavir‑ritonavir gp and the NRTI-sparing gp than in the efavirenz gp (P = 0.01 for the both comparisons by the Wilcoxon rank-sum test). At wk 48, there were no significant differences among the 3 gps in the change from baseline in the CD4 cell count.
Pts who had virologic failure and ≥1 drug-resistance mutations (excluding minor protease mutation)	22 of 250 (9%)	16 of 253 (6%)	39 of 250 (16%)	P<0.05 for the comparison between the NRTI-sparing group and both the efavirenz group and the lopinavir‑ritonavir groups
NRTI-associated mutation M184V K65R	14 (30) 8 (17) 3 (7)	15 (19) 13 (17) 0	6 (11) 1 (2) 0	Ef vs. NRTI-sp: 0.02 Ef vs. NRTI-sp: 0.01; NRTI-sp vs. lop p<0.01 Lop vs. ef 0.05
Thymidine analogue‑associated mutation (41L, 67N, 70R, 210W, 215Y/F, and 219Q/E were evaluated)	2 (4)	1 (1)	2 (4)	NS
NNRTI-associated mutation K103N	20 (43) 11 (24)	2 (3) 0	37 (66) 31 (55)	Ef vs. NRTI-sp: 0.03; lop vs. ef <0.001; NRTI-sp vs. lop <0.001 Ef vs. NRTI-sp: 0.002; lop vs. ef <0.001; NRTI-sp vs. lop <0.001
Any protease mutation	39 (85)	61 (78)	45 (80)	NS
Major protease mutation(30N, 32I, 33F, 46I, 47A/V, 48V, 50L/V, 82A/F/L/S/T, 84V, and 90M were evaluated)	0	0	2 (4)	NS
Mutation associated with two drug classes (only major	12 (26)	1 (1)	4 (7)	Ef vs. NRTI-sp: 0.01; Lop vs. ef <0.001; NRTI-sp vs. lop NS

protease mutations)				

Other outcomes:

Treatment-limiting events, as Adverse events are those that occurred in 3% or more of patients in any study group. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

Event n (%)	**Efavirenz group; n=250**	**Lopinavir–ritonavir group n=253**	**NRTI-sparing group n=250**
Treatment-limiting event (determined by the site investigator; defined as those occurring in ≥2% pts in any study group)			
Pain or discomfort	10 (4)	5 (2)	3 (1)
Fasting triglycerides*	0	4 (2)	11 (4)
Macules, papules, or rash**	6 (2)	0	3 (1)
Nausea	3 (1)	7 (3)	3 (1)
Grade 3 or 4 clinical event			
Any new sign or symptom	42 (17)	46 (18)	43 (17)
Pain or discomfort	14 (6)	14 (6)	19 (8)
Diarrhoea or loose stool**	1 (<1)	8 (3)	7 (3)
Nausea	7 (3)	4 (2)	8 (3)
Macules, papules, or rash	6 (2)	2 (1)	7 (3)
Headache	6 (2)	9 (4)	2 (1)
Grade 3 or 4 laboratory abnormality			
Any abnormality* §	72 (29)	80 (32)	107 (43)
Creatine kinase >5 times ULN	8 (3)	8 (3)	14 (6)
Absolute neutrophil count <750/mm^3	11 (4)	18 (7)	12 (5)
Fasting LDL cholesterol >190 mg/dl§	7 (3)	2 (1)	14 (6)
Fasting triglycerides >750 mg/dl* ** §	6 (2)	16 (6)	34 (14)
Aspartate aminotransferase, alanine aminotransferase or both >5 times ULN *	10 (4)	16 (6)	21 (8)
Lipase >2 times ULN **	22 (9)	11 (4)	12 (5)
Clinical lipoatrophy any grade *	8 (3)	3 (1)	0
Deaths probably associated with a study drug	0	0	1 (hepato-toxicity)

Median increase in limb fat as seen on DEXA from baseline to week 96 (P≤0.01 for each of the three pairwise comparisons)	0.05 kg	0.7 kg	1.15 kg
One or more new or recurrent conditions that define the presence of the acquired immunodeficiency syndrome (AIDS); differences were not significant	9/250 (4%)	16/253 (6%)	15/250 (6%)

*P<0.05 for the pairwise comparison between the efavirenz group and the NRTI-sparing group, with no adjustment for multiple testing

** P<0.05 for the pairwise comparison between the efavirenz group and the lopinavir‑ritonavir group, with no adjustment for multiple testing.

§ P<0.05 for the pairwise comparison between the lopinavir‑ritonavir group and the NRTI-sparing group, with no adjustment for multiple testing.

Stein 2008 substudy:

Changes in Lipids and Lipoproteins after 24 weeks of Antiretroviral Therapy: median (interquartile range)

	All	NRTIs + Efavirenz (PI-Sparing)	NRTIs + Lopinavir/ ritonavir (NNRTI-Sparing)	Efavirenz + Lopinavir/ ritonavir (NRTI-Sparing)	P_{KW} (Kruskal-Wallis) comparing all groups
Lipids					
Total cholesterol, mg/dL	27* (8 – 67)	18* (3 – 29)	21* (6 – 57)	65* (32 – 108)	<0.001
Triglycerides, mg/dL	44* (-4 – 126)	22 (-49 – 79)	72* (-1 – 186)	83* (11 – 164)	0.051
Direct LDL cholesterol, mg/dL	10*(-3 – 31)	6 (-5 – 24)	7 (-8 – 19)	26* (11 – 54)	<0.001
HDL cholesterol, mg/dL	9*(2 – 14)	9* (5 – 15)	3# (-1 – 13)	11* (7 – 17)	0.053
Total/HDL cholesterol ratio	-0.28 (-0.75 – 0.88)	-0.58* (-1.64 – -0.02)	0.02 (-0.99 – 1.29)	0.01 (-0.51 – 1.43)	0.017
Lipoproteins					
VLDL particles, nmol/L	29.6*(1.2 - 60.4)	13 (-16.6 - 33.4)	26.3* (2.8 - 60.3)	48.3* (14.2 - 84.4)	0.022
Large VLDL particles, nmol/L	1.1*(-0.2 - 6.7)	0.3 (-0.7 - 2.2)	3.2* (0.0 - 10.3)	1.2* (-0.1 - 11.3)	0.063
VLDL size, nm	3.2# (-5.2 - 11.1)	-0.2 (-5.2 - 7.4)	5.4# (-1.8 - 12.3)	2.6 (-10.4 - 12.4)	0.372
IDL particles, nmol/L	2 (-28 - 40)	-3 (-28 - 11)	-8 (-39 - 36)	18# (-5 - 76)	0.036
LDL particles, nmol/L	152* (-49 - 407)	64 (-65 - 167)	135# (-115 – 312)	414* (120 - 740)	0.003
Small LDL particles, nmol/L	130* (-98 - 417)	101 (-162 - 207)	127 (-162 – 357)	371* (-9 - 720)	0.039
LDL size, nm	-0.1 (-0.5 - 0.4)	0 (-0.3 - 0.6)	-0.1 (-0.6 - 0.4)	-0.3 (-0.5 - 0.1)	0.134
Lipoprotein (a), mg/ dL	5* (0-33)	3# (0-20)	4* (0 – 28)	7* (2 – 41)	0.309
HDL particles, µmol/L	6.0* (2.8 - 10.4)	5.3* (2.4 - 9.3)	5.1* (1.6 - 9.7)	8.3* (5.9 - 10.8)	0.069
Large HDL particles, µmol/L	0.5* (-0.9 - 2.8)	1.1 (-0.5 - 2.5)	0.1 (-1.1 - 2.6)	1.3# (-0.8 - 3.0)	0.663
HDL size, nm	0.1 (-0.2 - 0.3)	0.1 (-0.1 - 0.3)	0 (-0.2 - 0.4)	0.1 (-0.2 - 0.4)	0.799

Increase in BMI, kg/m2	0.5 (-0.5 – +1.9)				similar in each arm; pKW=0.68
Waist circumference, cm	1.0 (-1.80 – 4.0)				0.910
Increases in glucose levels		+4 (0 – +9), p<0.05 from baseline	not stated	+5 (-3 – +12), p<0.05 from baseline	0.04

* p<0.01 compared to baseline, Wilcoxon signed rank probability test
# 0.01≤p<0.05 compared to baseline, Wilcoxon signed rank probability test

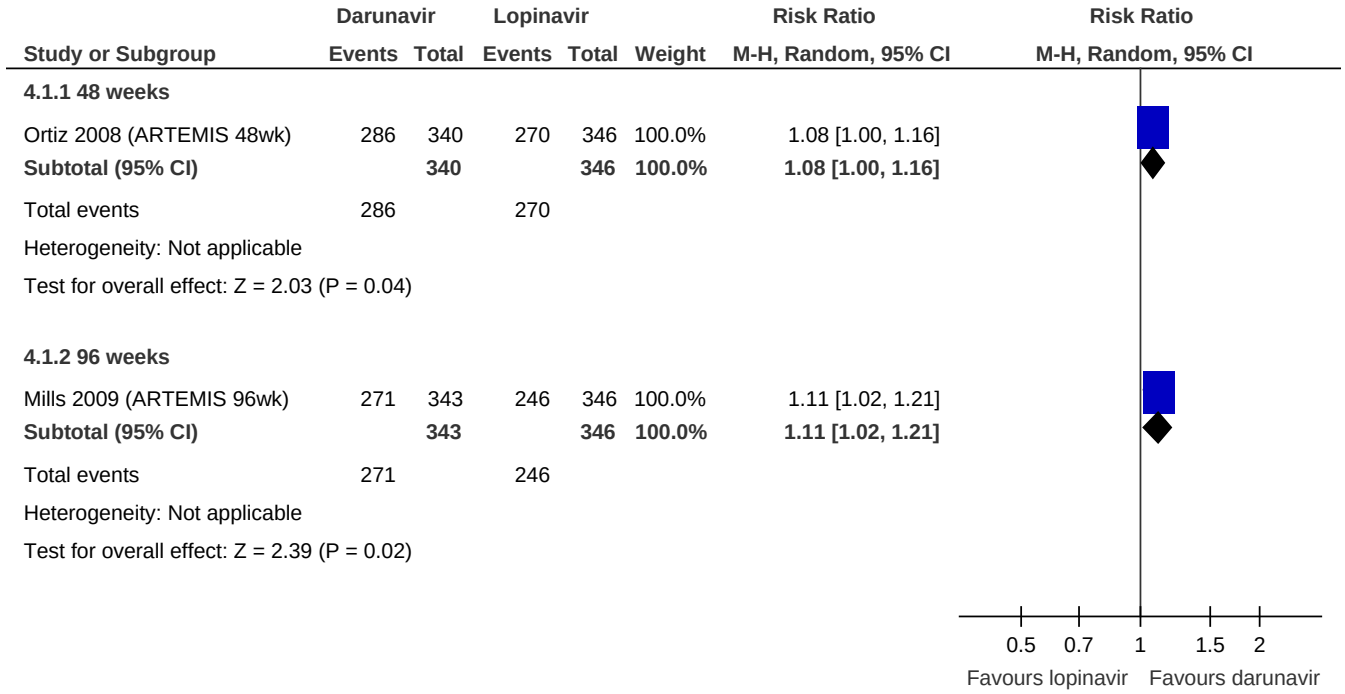
Authors' conclusion

Our study establishes the use of efavirenz plus two NRTIs as being more effective than lopinavir‑ ritonavir plus two NRTIs for initial therapy of HIV-1 infection, although the margin of superiority was moderate. Drug resistance was not a common outcome overall, but failure of efavirenz plus two NRTIs was often associated with NNRTI resistance, whereas failure of lopinavir‑ritonavir plus two NRTIs was not associated with lopinavir resistance, and NRTI resistance was similar in the two groups. These results highlight the complexity of choosing initial therapy. Selection of initial therapy for an individual patient should take into consideration many factors, including virologic and immunologic response, tolerability, short-term and long-term toxicity, and the resistance consequences associated with virologic failure.

In this prospective study with randomized assignment to three class-sparing ART regimens, significant lipoprotein changes were observed. Total and small LDL particle concentrations increased, especially in the arms containing the PI lopinavir/ritonavir, as did total VLDL particles. HDL particles increased to a similar extent in all arms. Adverse changes in LDL and IDL were especially prominent in the arm with efavirenz + lopinavir/ritonavir. These changes were not related to changes in markers of insulin/glucose metabolism.

Forest plots Darunavir vs. lopinavir/r

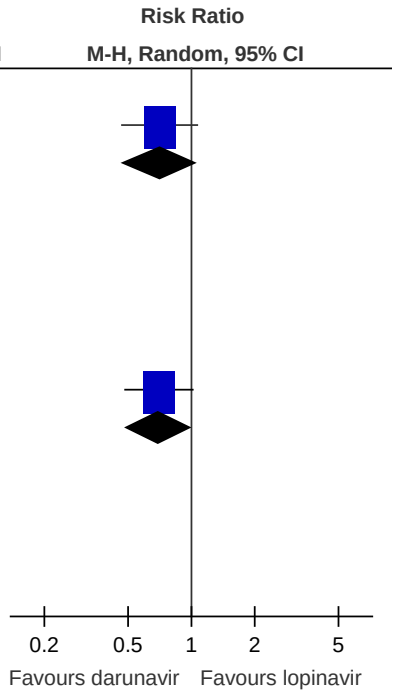
Viral suppression <50 copies/mL.



Viral suppression <50 copies/mL favours darunavir over lopinavir.

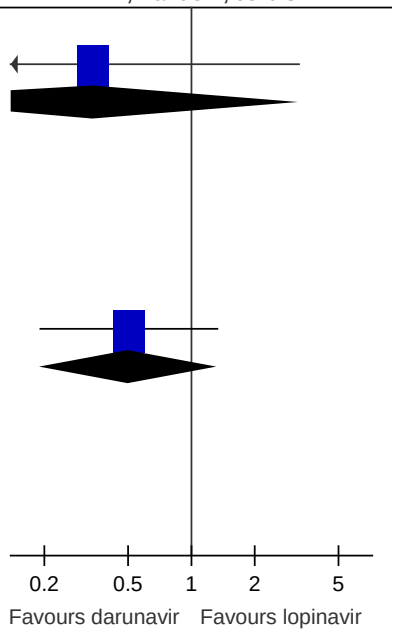
Virological failure.

Study or Subgroup	Darunavir Events	Darunavir Total	Lopinavir Events	Lopinavir Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 48 weeks						
Ortiz 2008 (ARTEMIS 48wk)	34	340	49	346	100.0%	0.71 [0.47, 1.07]
Subtotal (95% CI)		**340**		**346**	**100.0%**	**0.71 [0.47, 1.07]**
Total events	34		49			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.66 (P = 0.10)						
4.2.2 96 weeks						
Mills 2009 (ARTEMIS 96wk)	41	343	59	346	100.0%	0.70 [0.48, 1.01]
Subtotal (95% CI)		**343**		**346**	**100.0%**	**0.70 [0.48, 1.01]**
Total events	41		59			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.88 (P = 0.06)						

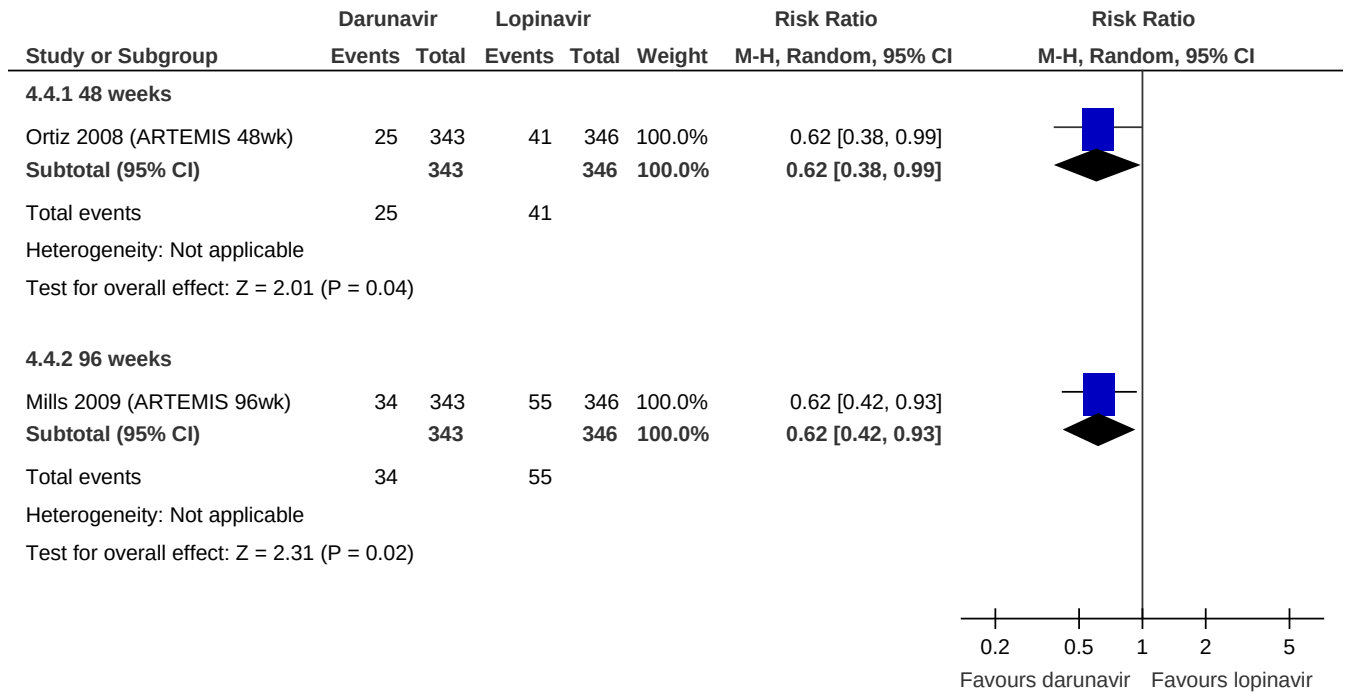


Drug resistance.

Study or Subgroup	Darunavir Events	Darunavir Total	Lopinavir Events	Lopinavir Total	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 48 weeks						
Ortiz 2008 (ARTEMIS 48wk)	1	340	3	346	100.0%	0.34 [0.04, 3.24]
Subtotal (95% CI)		**340**		**346**	**100.0%**	**0.34 [0.04, 3.24]**
Total events	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.94 (P = 0.35)						
4.3.2 96 weeks						
Mills 2009 (ARTEMIS 96wk)	6	343	12	346	100.0%	0.50 [0.19, 1.33]
Subtotal (95% CI)		**343**		**346**	**100.0%**	**0.50 [0.19, 1.33]**
Total events	6		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.39 (P = 0.17)						



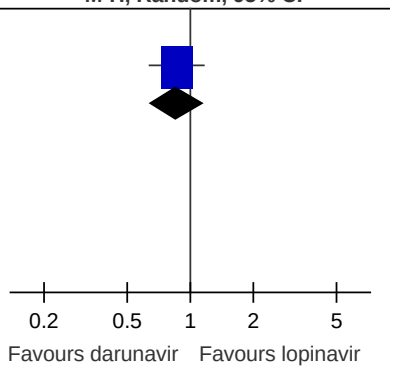
Serious adverse event.



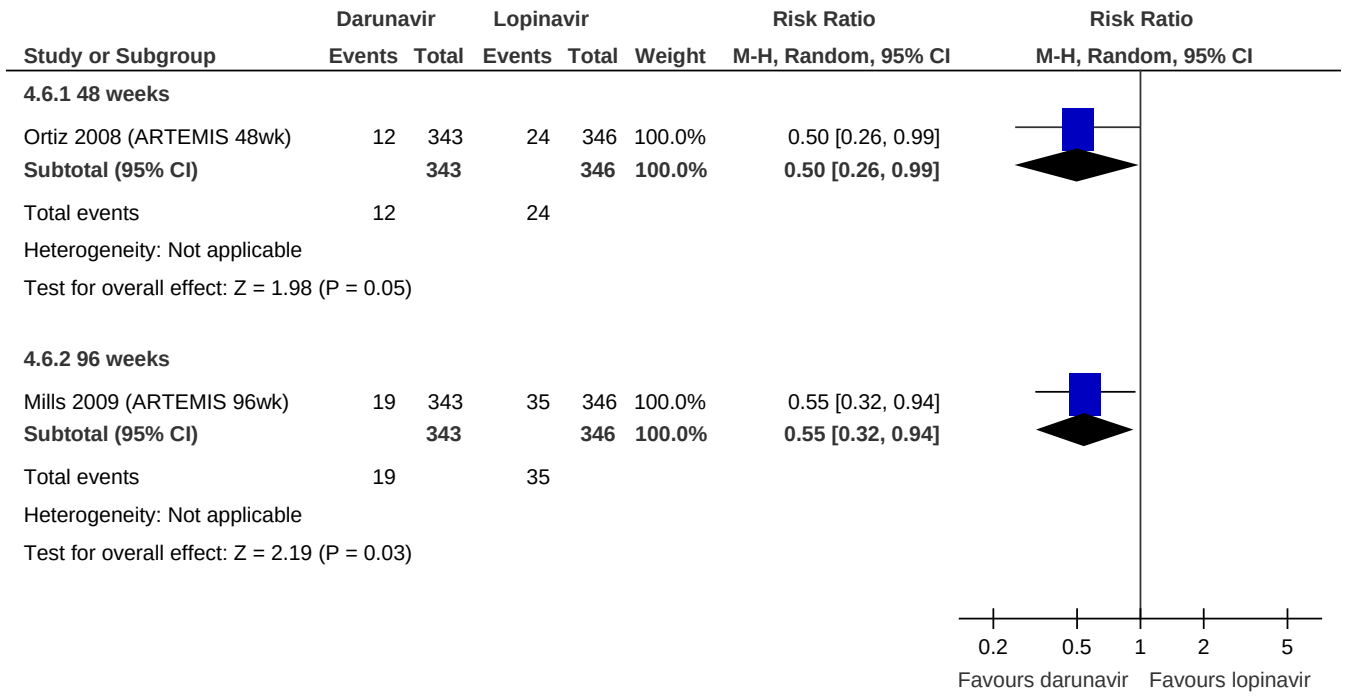
Serious adverse event favours darunavir over lopinavir.

Grade 3 or 4 adverse event.

Study or Subgroup	Darunavir Events	Darunavir Total	Lopinavir Events	Lopinavir Total	Weight	Risk Ratio M-H, Random, 95% CI
4.5.1 48 weeks						
Ortiz 2008 (ARTEMIS 48wk)	64	343	75	346	100.0%	0.86 [0.64, 1.16]
Subtotal (95% CI)		**343**		**346**	**100.0%**	**0.86 [0.64, 1.16]**
Total events	64		75			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						



Discontinuation due to adverse event.



Discontinuation due to adverse event favours darunavir over lopinavir.

NNT/NNH table for darunavir versus lopinavir

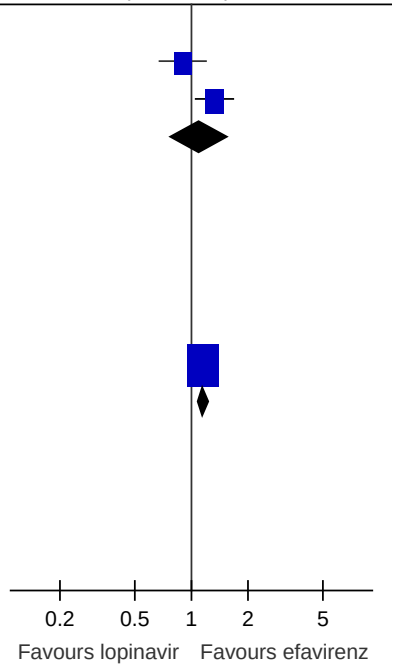
	darunavir better	lopinavir better	ARR	NNT
Viral suppression <50 copies/mL	yes	no	78/1000	13
Serious adverse event	yes	no	45/1000	
Discontinuation due to adverse event	yes	no	35/1000	

13 people would need to be treated with darunavir rather than lopinavir to gain 1 extra person with viral suppression.

Forest plots lopinavir/r vs. efavirenz

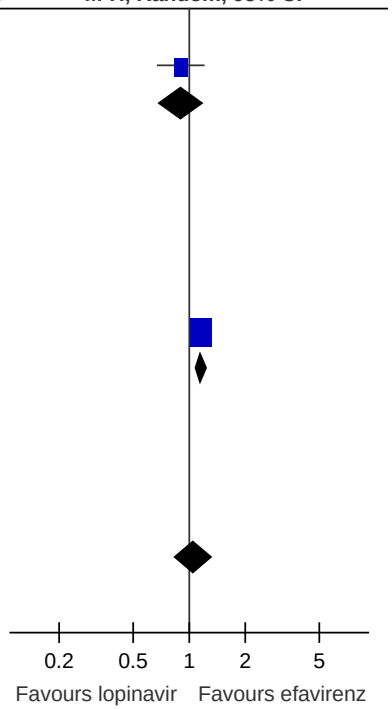
Viral suppression < 50 copies/mL

	Efavirenz		Lopinavir			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
5.1.1 48 weeks							
Echeverria 2010 (LAKE48w)	36	63	40	63	47.6%	0.90 [0.68, 1.20]	
Sierra-Madero 2010 (48wk)	67	95	50	94	52.4%	1.33 [1.05, 1.67]	
Subtotal (95% CI)		**158**		**157**	**100.0%**	**1.10 [0.75, 1.61]**	
Total events	103		90				
Heterogeneity: Tau² = 0.06; Chi² = 4.31, df = 1 (P = 0.04); I² = 77%							
Test for overall effect: Z = 0.51 (P = 0.61)							
5.1.2 96 weeks							
Riddler 2008 (5142 96wk)	223	250	195	253	100.0%	1.16 [1.07, 1.25]	
Subtotal (95% CI)		**250**		**253**	**100.0%**	**1.16 [1.07, 1.25]**	
Total events	223		195				
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.59 (P = 0.0003)							



Sensitivity analysis for viral suppression excluding Sierra-Madero 2010 (due to heterogeneity of population)

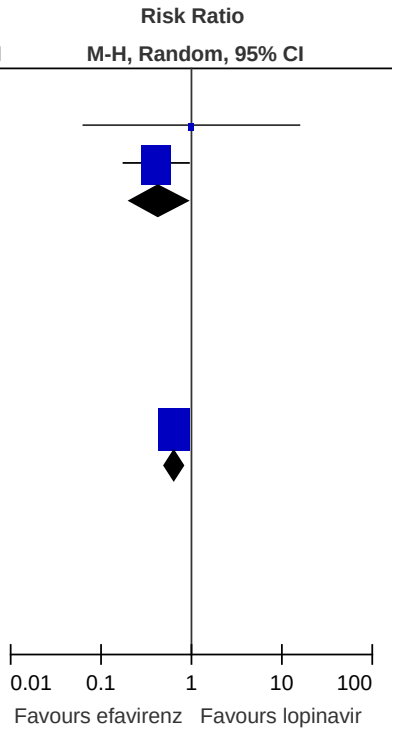
Study or Subgroup	Efavirenz Events	Efavirenz Total	Lopinavir Events	Lopinavir Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 48 weeks						
Echeverria 2010 (LAKE48w)	36	63	40	63	36.0%	0.90 [0.68, 1.20]
Subtotal (95% CI)		**63**		**63**	**36.0%**	**0.90 [0.68, 1.20]**
Total events	36		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
6.1.2 96 weeks						
Riddler 2008 (5142 96wk)	223	250	195	253	64.0%	1.16 [1.07, 1.25]
Subtotal (95% CI)		**250**		**253**	**64.0%**	**1.16 [1.07, 1.25]**
Total events	223		195			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.59 (P = 0.0003)						
Total (95% CI)		**313**		**316**	**100.0%**	**1.06 [0.83, 1.35]**
Total events	259		235			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.06$, df = 1 (P = 0.08); $I^2 = 67\%$						
Test for overall effect: Z = 0.44 (P = 0.66)						



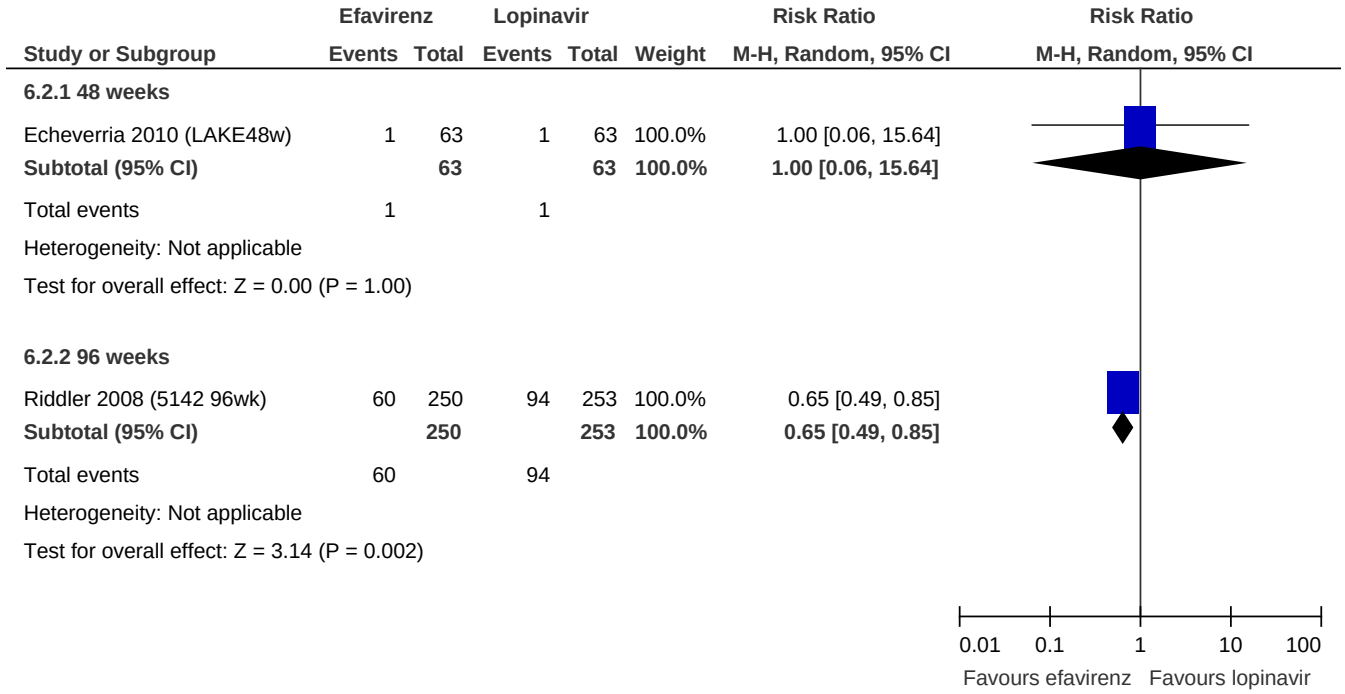
Heterogeneity between 48 and 96 week results.

Virological failure.

Study or Subgroup	Efavirenz Events	Efavirenz Total	Lopinavir Events	Lopinavir Total	Weight	Risk Ratio M-H, Random, 95% CI
5.2.1 48 weeks						
Echeverria 2010 (LAKE48w)	1	63	1	63	8.4%	1.00 [0.06, 15.64]
Sierra-Madero 2010 (48wk)	7	95	17	94	91.6%	0.41 [0.18, 0.94]
Subtotal (95% CI)		**158**		**157**	**100.0%**	**0.44 [0.20, 0.97]**
Total events	8		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 1 (P = 0.54); I² = 0%						
Test for overall effect: Z = 2.02 (P = 0.04)						
5.2.2 96 weeks						
Riddler 2008 (5142 96wk)	60	250	94	253	100.0%	0.65 [0.49, 0.85]
Subtotal (95% CI)		**250**		**253**	**100.0%**	**0.65 [0.49, 0.85]**
Total events	60		94			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.14 (P = 0.002)						



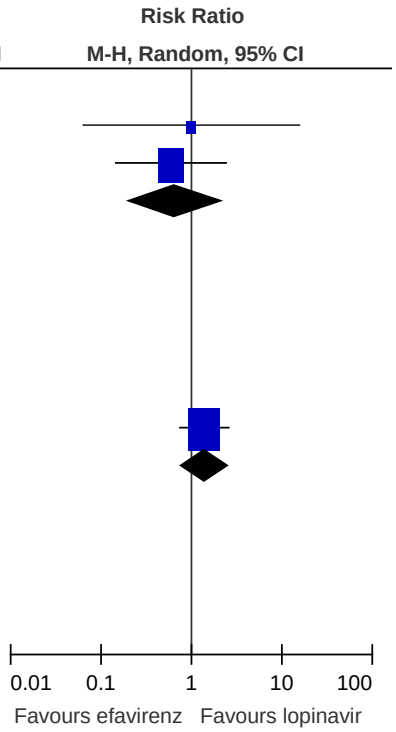
Sensitivity analysis for virological failure excluding Sierra-Madero 2010 (due to heterogeneity of population)



Virological failure favours efavirenz over lopinavir.

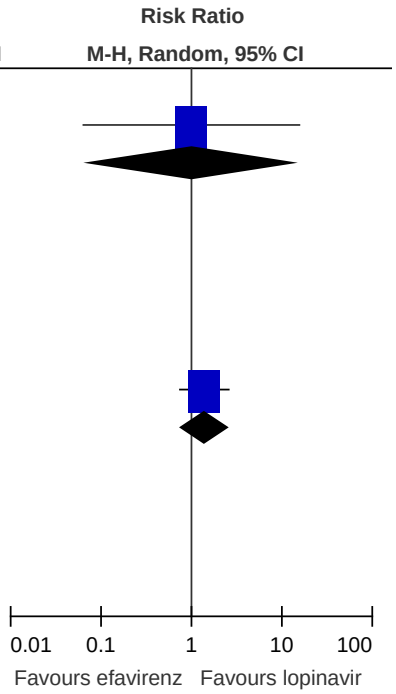
Drug resistance.

Study or Subgroup	Efavirenz Events	Efavirenz Total	Lopinavir Events	Lopinavir Total	Weight	Risk Ratio M-H, Random, 95% CI
5.3.1 48 weeks						
Echeverria 2010 (LAKE48w)	1	63	1	63	20.6%	1.00 [0.06, 15.64]
Sierra-Madero 2010 (48wk)	3	95	5	94	79.4%	0.59 [0.15, 2.41]
Subtotal (95% CI)		**158**		**157**	**100.0%**	**0.66 [0.19, 2.31]**
Total events	4		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.65 (P = 0.52)						
5.3.2 96 weeks						
Riddler 2008 (5142 96wk)	22	250	16	253	100.0%	1.39 [0.75, 2.59]
Subtotal (95% CI)		**250**		**253**	**100.0%**	**1.39 [0.75, 2.59]**
Total events	22		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						



Sensitivity analysis for drug resistance excluding Sierra-Madero 2010 (due to heterogeneity of population)

Study or Subgroup	Efavirenz Events	Total	Lopinavir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
6.3.1 48 weeks						
Echeverria 2010 (LAKE48w)	1	63	1	63	100.0%	1.00 [0.06, 15.64]
Subtotal (95% CI)		**63**		**63**	**100.0%**	**1.00 [0.06, 15.64]**
Total events	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
6.3.2 96 weeks						
Riddler 2008 (5142 96wk)	22	250	16	253	100.0%	1.39 [0.75, 2.59]
Subtotal (95% CI)		**250**		**253**	**100.0%**	**1.39 [0.75, 2.59]**
Total events	22		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						

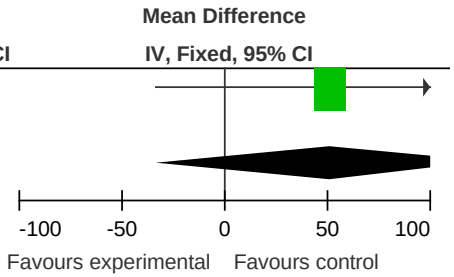


CD4 cell count.

Study or Subgroup	Efavirenz Mean	SD	Total	Lopinavir Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Echeverria 2010 (LAKE48w)	491	244	63	440	240	63	100.0%	51.00 [-33.51, 135.51]
Total (95% CI)			**63**			**63**	**100.0%**	**51.00 [-33.51, 135.51]**

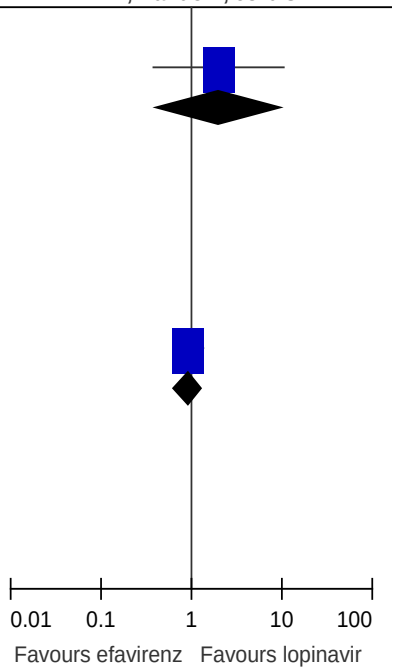
Heterogeneity: Not applicable

Test for overall effect: Z = 1.18 (P = 0.24)



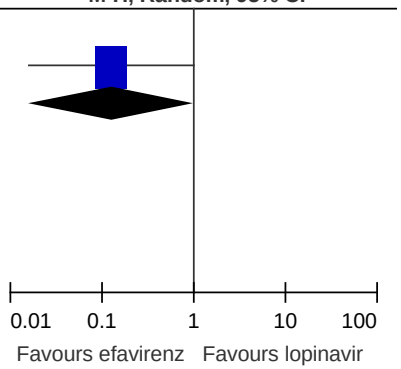
Grade 3 or 4 clinical adverse events

Study or Subgroup	Efavirenz Events	Efavirenz Total	Lopinavir Events	Lopinavir Total	Weight	Risk Ratio M-H, Random, 95% CI
5.5.1 48 weeks						
Echeverria 2010 (LAKE48w)	4	63	2	63	100.0%	2.00 [0.38, 10.53]
Subtotal (95% CI)		**63**		**63**	**100.0%**	**2.00 [0.38, 10.53]**
Total events	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
5.5.2 96 weeks						
Riddler 2008 (5142 96wk)	42	250	46	253	100.0%	0.92 [0.63, 1.35]
Subtotal (95% CI)		**250**		**253**	**100.0%**	**0.92 [0.63, 1.35]**
Total events	42		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						



Grade 3 or 4 diarrhoea

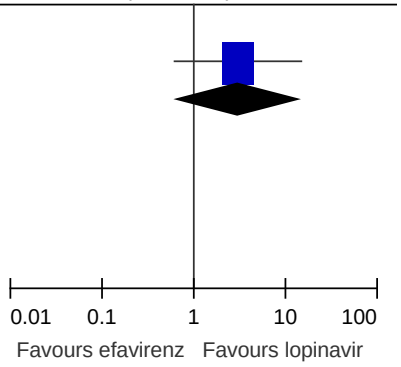
	Efavirenz		Lopinavir			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
5.6.2 96 weeks							
Riddler 2008 (5142 96wk)	1	250	8	253	100.0%	0.13 [0.02, 1.00]	
Subtotal (95% CI)		**250**		**253**	**100.0%**	**0.13 [0.02, 1.00]**	
Total events	1		8				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.96 (P = 0.05)							



Grade 3 or 4 diarrhoea favours efavirenz over lopinavir.

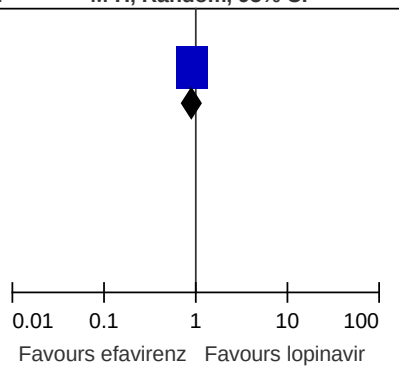
Grade 3 or 4 rash.

	Efavirenz		Lopinavir			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
5.7.2 96 weeks							
Riddler 2008 (5142 96wk)	6	250	2	253	100.0%	3.04 [0.62, 14.90]	
Subtotal (95% CI)		**250**		**253**	**100.0%**	**3.04 [0.62, 14.90]**	
Total events	6		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.37 (P = 0.17)							



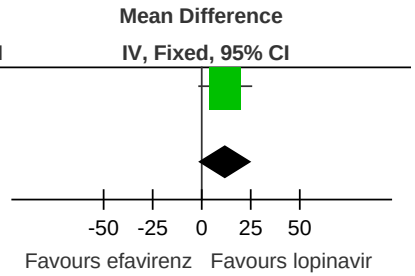
Grade 3 or 4 laboratory adverse event.

Study or Subgroup	Efavirenz Events	Efavirenz Total	Lopinavir Events	Lopinavir Total	Weight	Risk Ratio M-H, Random, 95% CI
5.8.2 96 weeks						
Riddler 2008 (5142 96wk)	72	250	80	253	100.0%	0.91 [0.70, 1.19]
Subtotal (95% CI)		**250**		**253**	**100.0%**	**0.91 [0.70, 1.19]**
Total events	72		80			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						



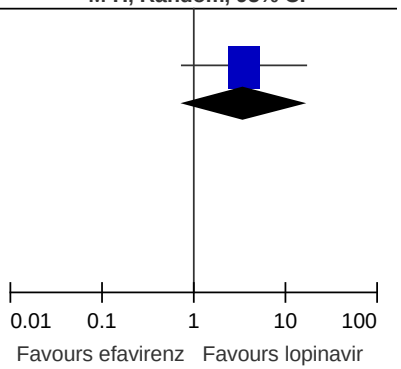
Total cholesterol.

Study or Subgroup	Efavirenz Mean	Efavirenz SD	Efavirenz Total	Lopinavir Mean	Lopinavir SD	Lopinavir Total	Weight	Mean Difference IV, Fixed, 95% CI
Echeverria 2010 (LAKE48w)	205	28	63	193	46	63	100.0%	12.00 [-1.30, 25.30]
Total (95% CI)			**63**			**63**	**100.0%**	**12.00 [-1.30, 25.30]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.77 (P = 0.08)								



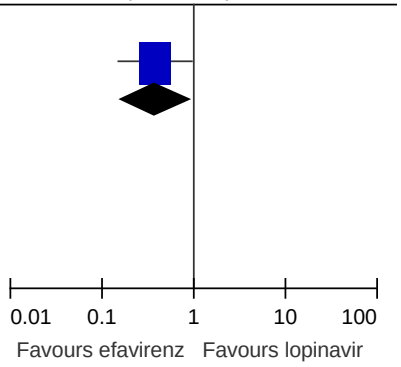
Grade 3 or 4 LDL cholesterol.

Study or Subgroup	Efavirenz Events	Total	Lopinavir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.10.2 96 weeks						
Riddler 2008 (5142 96wk)	7	250	2	253	100.0%	3.54 [0.74, 16.88]
Subtotal (95% CI)		**250**		**253**	**100.0%**	**3.54 [0.74, 16.88]**
Total events	7		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.59 (P = 0.11)						



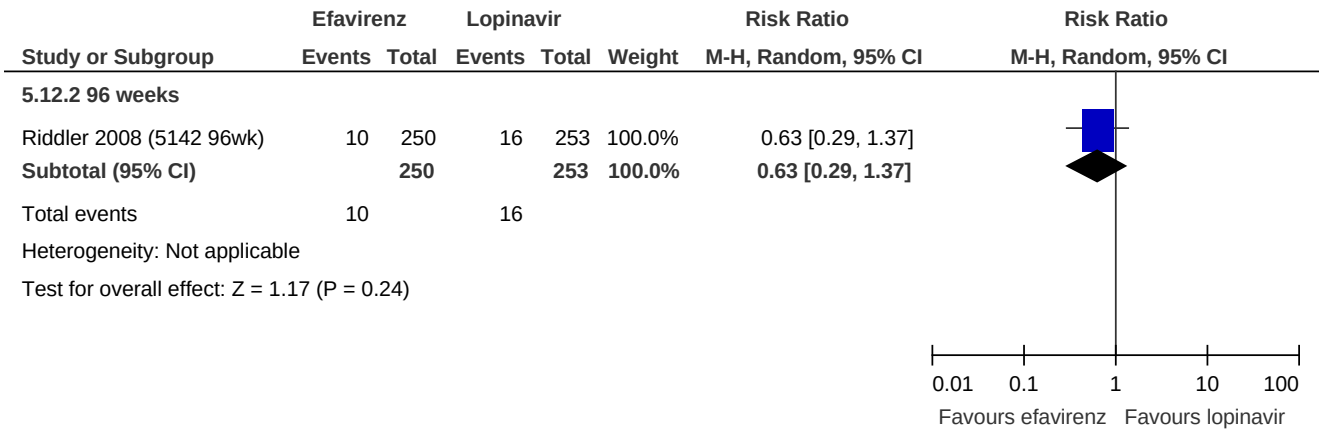
Grade 3 or 4 triglycerides.

Study or Subgroup	Efavirenz Events	Total	Lopinavir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.11.2 96 weeks						
Riddler 2008 (5142 96wk)	6	250	16	253	100.0%	0.38 [0.15, 0.95]
Subtotal (95% CI)		**250**		**253**	**100.0%**	**0.38 [0.15, 0.95]**
Total events	6		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.06 (P = 0.04)						



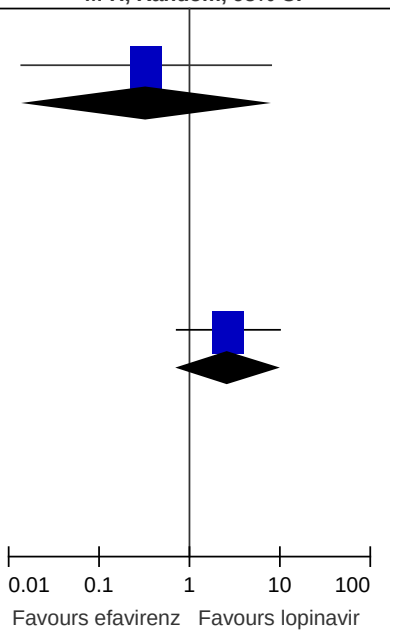
Grade 3 or 4 triglycerides favours efavirenz over lopinavir.

Grade 3 or 4 AST or ALT.

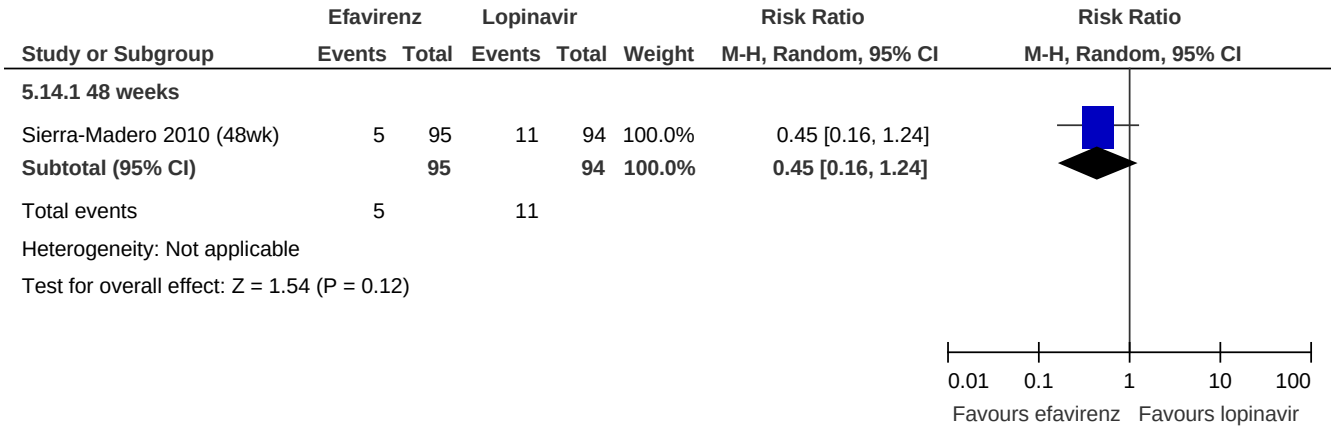


Lipodystrophy.

Study or Subgroup	Efavirenz Events	Efavirenz Total	Lopinavir Events	Lopinavir Total	Weight	Risk Ratio M-H, Random, 95% CI
5.13.1 48 weeks						
Echeverria 2010 (LAKE48w)	0	63	1	63	100.0%	0.33 [0.01, 8.03]
Subtotal (95% CI)		**63**		**63**	**100.0%**	**0.33 [0.01, 8.03]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
5.13.2 96 weeks						
Riddler 2008 (5142 96wk)	8	250	3	253	100.0%	2.70 [0.72, 10.06]
Subtotal (95% CI)		**250**		**253**	**100.0%**	**2.70 [0.72, 10.06]**
Total events	8		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						



Discontinuation due to adverse event.



Excluding Sierra-Madero 2010 (due to heterogeneity of population) gives no data for this outcome.

NNT/NNH table for Efavirenz versus lopinavir

	Efavirenz better	Lopinavir better	ARR	NNT
Virological failure	yes	no	130/1000	8
Grade 3 or 4 diarrhoea	yes	no	28/1000	
Grade 3 or 4 triglycerides	yes	no	39/1000	

8 people would need to be treated with efavirenz rather than lopinavir to avoid 1 case of virological failure

Direct comparisons:

Comparison	Which drug is more effective?	NNT*	Which drug is safer?	NNH**
Efavirenz vs atazanavir	equally effective	-	Atazanavir better for the outcomes of drug resistance, grade 3/4 neurological events, grade 3/4 total cholesterol and grade 3/4 LDL cholesterol	20
Efavirenz vs rilpirivine	equally effective	-	25 people would need to be treated with efavirenz rather than rilpivirine to avoid 1 case of drug resistance. But this is at the expense of more laboratory adverse events and discontinuations due to adverse events. If 1000 people were treated with efavirenz rather than rilpivirine, there would be 40 fewer cases of drug resistance, but 67 more grade 3 or 4 laboratory adverse events and 43 more discontinuations due to adverse events.	trade-off between adverse events; NNH cannot be calculated
Efavirenz vs raltegravir	equally effective	-	raltegravir better for Grade 3/4 LDL cholesterol and Grade 3 or 4 triglycerides	20
Darunavir vs lopinavir	Viral suppression <50 copies/mL favours darunavir over lopinavir.	13	Darunavir better (fewer serious adverse events and 35 fewer discontinuations due to adverse events)	
Efavirenz vs lopinavir	Virological failure favours efavirenz over lopinavir.	8	Efavirenz better (grade 3 or 4 diarrhoea and 39 fewer with grade 3 or 4 triglyceride adverse events)	

* large NNT means a lot of people need to be treated to see a difference between the drugs on efficacy (i.e. difference between drugs small); - means no significant difference between drugs

** large NNH means a lot of people need to be treated to see a difference between the drugs on safety (i.e. difference between drugs small)

Efavirenz vs darunavir (indirect comparison)

If 1000 people were treated with darunavir rather than lopinavir, there would be 78 more people with viral suppression, 45 fewer serious adverse events and 35 fewer discontinuations due to adverse events.

If 1000 people were treated with efavirenz rather than lopinavir, there would be 130 fewer people with virological failure, 28 fewer with grade 3 or 4 diarrhoea and 39 fewer with grade 3 or 4 triglyceride adverse events.

The choice between efavirenz and darunavir therefore depends on the relative weight given to each outcome.

GRADE tables:

A Efavirenz versus atazanavir

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Efavirenz versus atazanavir	control	Relative (95% CI)	Absolute		
Viral suppression <50 copies week 48												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	97/108 (89.8%)	93/101 (92.1%) 92.1%	RR 0.98 (0.9 to 1.06)	18 fewer per 1000 (from 92 fewer to 55 more) 18 fewer per 1000 (from 92 fewer to 55 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Virological failure - Week 48												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	112/1043 (10.7%)	115/1033 (11.1%) 7.9%	RR 0.97 (0.76 to 1.24)	3 fewer per 1000 (from 27 fewer to 27 more) 2 fewer per 1000 (from 19 fewer to 19 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Virological failure - Week 96												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	129/929 (13.9%)	140/928 (15.1%) 15.1%	RR 0.92 (0.74 to 1.15)	12 fewer per 1000 (from 39 fewer to 23 more) 12 fewer per 1000 (from 39 fewer to 23 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Drug resistance (follow-up 96 weeks)												
2	randomised	no serious	no serious	no serious	no serious	none	71/1036 (6.9%)	18/1031	RR 3.94 (2.37	51 more per 1000 (from	⊕⊕⊕⊕	CRITICAL

	trials	limitations	inconsistency	indirectness	imprecision			(1.7%) 1.4%	to 6.56)	24 more to 97 more) 41 more per 1000 (from 19 more to 78 more)	HIGH	
Serious adverse event (follow-up 48 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	14/114 (12.3%)	8/105 (7.6%) 7.6%	RR 1.61 (0.7 to 3.69)	46 more per 1000 (from 23 fewer to 205 more) 46 more per 1000 (from 23 fewer to 204 more)	⊕⊕⊕O MODERATE	CRITICAL
Grade 3 or 4 adverse event (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	334/929 (36%)	311/928 (33.5%) 33.5%	RR 1.07 (0.95 to 1.22)	23 more per 1000 (from 17 fewer to 74 more) 23 more per 1000 (from 17 fewer to 74 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Grade 3 or 4 neuropsychological event (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	56/922 (6.1%)	24/926 (2.6%) 2.6%	RR 2.34 (1.47 to 3.75)	35 more per 1000 (from 12 more to 71 more) 35 more per 1000 (from 12 more to 71 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Grade 3 or 4 diarrhoea (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/922 (1.8%)	13/926 (1.4%) 1.4%	RR 1.31 (0.64 to 2.69)	4 more per 1000 (from 5 fewer to 24 more) 4 more per 1000 (from 5 fewer to 24 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Grade 3 or 4 AST elevation (follow-up 96 weeks)												

1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/922 (1.3%)	20/926 (2.2%) 2.2%	RR 0.6 (0.3 to 1.23)	9 fewer per 1000 (from 15 fewer to 5 more) 9 fewer per 1000 (from 15 fewer to 5 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Grade 3 or 4 ALT elevation (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/922 (1.5%)	18/926 (1.9%) 1.9%	RR 0.78 (0.39 to 1.56)	4 fewer per 1000 (from 12 fewer to 11 more) 4 fewer per 1000 (from 12 fewer to 11 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Grade 3 or 4 total cholesterol (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	28/922 (3%)	13/926 (1.4%) 1.4%	RR 2.16 (1.13 to 4.15)	16 more per 1000 (from 2 more to 44 more) 16 more per 1000 (from 2 more to 44 more)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Grade 3 or 4 LDL cholesterol (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	44/922 (4.8%)	21/926 (2.3%) 2.3%	RR 2.1 (1.26 to 3.51)	25 more per 1000 (from 6 more to 57 more) 25 more per 1000 (from 6 more to 58 more)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Grade 3 or 4 triglycerides (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/922 (2.4%)	23/926 (2.5%) 2.5%	RR 0.96 (0.54 to 1.71)	1 fewer per 1000 (from 11 fewer to 18 more) 1 fewer per 1000 (from 12 fewer to 18 more)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT

Renal failure (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/922 (0.9%)	10/926 (1.1%) 1.1%	RR 0.8 (0.32 to 2.03)	2 fewer per 1000 (from 7 fewer to 11 more) 2 fewer per 1000 (from 7 fewer to 11 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in lumbar spine BMD (%, 0-96 weeks) (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	107	91	-	MD 1.55 higher (0.22 to 2.88 higher)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Change in lumbar spine BMD (%, 0-96 weeks) - With TDF (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	54	43	-	MD 1.86 higher (0.02 to 3.7 higher)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Change in lumbar spine BMD (%, 0-96 weeks) - With ABC (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	53	48	-	MD 1.21 higher (0.72 lower to 3.14 higher)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Change in hip BMD (%, 0-96 weeks) (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	90	-	MD 0.33 higher (0.85 lower to 1.51 higher)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Change in hip BMD (%, 0-96 weeks) - With TDF (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	54	42	-	MD 0.62 higher (1.24 lower to 2.48 higher)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Change in hip BMD (%, 0-96 weeks) - With ABC (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	51	48	-	MD 0.14 higher (1.39 lower to 1.67 higher)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT

Bone fractures (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	43/922 (4.7%)	37/926 (4%) 4%	RR 1.17 (0.76 to 1.79)	7 more per 1000 (from 10 fewer to 32 more) 7 more per 1000 (from 10 fewer to 32 more)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Patients with 10% or more limb fat loss (week 96) (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/109 (16.5%)	15/94 (16%) 16%	RR 1.03 (0.55 to 1.94)	5 more per 1000 (from 72 fewer to 150 more) 5 more per 1000 (from 72 fewer to 150 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in limb fat (%, 0-96 weeks) (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	109	94	-	MD 13.63 lower (24.24 to 3.02 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in limb fat (%, 0-96 weeks) - With TDF (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	45	-	MD 12.5 lower (26.84 lower to 1.84 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in limb fat (%, 0-96 weeks) - With ABC (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	53	49	-	MD 15 lower (30.78 lower to 0.78 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in trunk fat (%, 0-96 weeks) (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	109	94	-	MD 15.34 lower (29.11 to 1.56 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in trunk fat (%, 0-96 weeks) - With TDF (Better indicated by higher values)												

1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	45	-	MD 15.8 lower (34.58 lower to 2.98 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in trunk fat (%, 0-96 weeks) - With ABC (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	53	49	-	MD 14.8 lower (35.06 lower to 5.46 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in visceral adipose tissue (%, 0-96 weeks) (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	90	-	MD 14.04 lower (28.89 lower to 0.81 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in visceral adipose tissue (%, 0-96 weeks) - With TDF (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	54	45	-	MD 14.7 lower (43.61 lower to 14.21 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in visceral adipose tissue (%, 0-96 weeks) - With ABC (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	51	45	-	MD 13.8 lower (31.11 lower to 3.51 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in visceral:total adipose tissue (%, 0-96 weeks) (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	90	-	MD 1.28 higher (4.41 lower to 6.97 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in visceral:total adipose tissue (%, 0-96 weeks) - With TDF (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	54	45	-	MD 2 higher (5.66 lower to 9.66 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in visceral:total adipose tissue (%, 0-96 weeks) - With ABC (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	51	45	-	MD 0.4 higher (8.09 lower to 8.89 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT

Cognitive speed score (lower = better) (follow-up 48 weeks; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9	8	-	MD 0 higher (0.07 lower to 0.07 higher)	⊕⊕⊕O MODERATE	NOT IMPORTANT
Cognitive accuracy score (higher = better) (follow-up 48 weeks; Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9	8	-	MD 0.14 lower (0.32 lower to 0.04 higher)	⊕⊕⊕O MODERATE	NOT IMPORTANT

[1] Wide confidence intervals
[2] Small sample size

B Efavirenz versus rilpirivine

Quality assessment							Summary of findings				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Efavirenz versus rilpirivine	control	Relative (95% CI)	Absolute		
Viral suppression <50 copies/mL (follow-up 48 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	561/682 (82.3%)	578/686 (84.3%) 84.3%	RR 0.98 (0.93 to 1.02)	17 fewer per 1000 (from 59 fewer to 17 more) 17 fewer per 1000 (from 59 fewer to 17 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Virological failure (follow-up 48 weeks)												
2	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	33/682 (4.8%)	62/686 (9%) 9%	RR 0.55 (0.29 to 1.02)	41 fewer per 1000 (from 64 fewer to 2 more) 40 fewer per 1000 (from 64 fewer to 2 more)	⊕⊕⊕O MODERATE	CRITICAL
Drug resistance (follow-up 8 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/682 (2.3%)	44/686 (6.4%) 6.4%	RR 0.38 (0.2 to 0.72)	40 fewer per 1000 (from 18 fewer to 51 fewer) 40 fewer per 1000 (from 18 fewer to 51 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse event (follow-up 48 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	55/682 (8.1%)	45/686 (6.6%)	RR 1.23 (0.84 to 1.8)	15 more per 1000 (from 10 fewer to 52 more)	⊕⊕⊕⊕	CRITICAL

								6.6%		15 more per 1000 (from 11 fewer to 53 more)	HIGH	
Grade 3 or 4 rash (follow-up 48 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	3/682 (0.4%)	1/686 (0.1%) 0.1%	RR 2.33 (0.34 to 15.83)	2 more per 1000 (from 1 fewer to 22 more) 1 more per 1000 (from 1 fewer to 15 more)	⊕⊕⊕O MODERATE	CRITICAL
Grade 3 or 4 laboratory adverse event (follow-up 48 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	118/670 (17.6%)	75/685 (10.9%) 11%	RR 1.61 (1.23 to 2.11)	67 more per 1000 (from 25 more to 122 more) 67 more per 1000 (from 25 more to 122 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Grade 3 or 4 AST (follow-up 48 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/669 (2.8%)	14/685 (2%) 2%	RR 1.39 (0.7 to 2.75)	8 more per 1000 (from 6 fewer to 36 more) 8 more per 1000 (from 6 fewer to 35 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Grade 3 or 4 ALT (follow-up 48 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/678 (3.4%)	10/685 (1.5%) 1.5%	RR 2.29 (1.09 to 4.8)	19 more per 1000 (from 1 more to 55 more) 19 more per 1000 (from 1 more to 57 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Grade 3 or 4 total cholesterol (follow-up 48 weeks)												
2	randomised	no serious	no serious	no serious	serious[2]	none	17/668 (2.5%)	1/685	RR 9.93 (1.83	13 more per 1000 (from 1	⊕⊕⊕O	NOT

	trials	limitations	inconsistency	indirectness				(0.1%) 0.1%	to 53.94)	more to 77 more) 9 more per 1000 (from 1 more to 53 more)	MODERATE	IMPORTANT
Grade 3 or 4 LDL cholesterol (follow-up 48 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	27/666 (4.1%)	5/685 (0.7%) 0.7%	RR 5 (1.38 to 18.17)	29 more per 1000 (from 3 more to 125 more) 28 more per 1000 (from 3 more to 120 more)	⊕⊕⊕O MODERATE	NOT IMPORTANT
Grade 3 or 4 triglycerides (follow-up 48 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	15/668 (2.2%)	2/685 (0.3%) 0.3%	RR 7.36 (1.67 to 32.39)	19 more per 1000 (from 2 more to 92 more) 19 more per 1000 (from 2 more to 94 more)	⊕⊕⊕O MODERATE	NOT IMPORTANT
Discontinuation due to adverse event (follow-up 48 weeks)												
2	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	52/682 (7.6%)	23/686 (3.4%) 3.4%	RR 2.29 (1.15 to 4.57)	43 more per 1000 (from 5 more to 120 more) 44 more per 1000 (from 5 more to 121 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] Heterogeneity between studies
[2] Wide confidence intervals

C Efavirenz versus raltegravir

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Efavirenz versus raltegravir	control	Relative (95% CI)	Absolute		
Viral suppression <50 copies/mL - 48 weeks												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	263/319 (82.4%)	378/440 (85.9%) 85.9%	RR 0.96 (0.9 to 1.03)	34 fewer per 1000 (from 86 fewer to 26 more) 34 fewer per 1000 (from 86 fewer to 26 more)	⊕⊕⊕O MODERATE	CRITICAL
Viral suppression <50 copies/mL - 96 weeks												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	255/320 (79.7%)	361/441 (81.9%) 82.1%	RR 0.98 (0.91 to 1.06)	16 fewer per 1000 (from 74 fewer to 49 more) 16 fewer per 1000 (from 74 fewer to 49 more)	⊕⊕⊕O MODERATE	CRITICAL
Virological failure - 96 weeks												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	47/320 (14.7%)	45/441 (10.2%) 8.8%	RR 1.16 (0.79 to 1.71)	16 more per 1000 (from 21 fewer to 72 more) 14 more per 1000 (from 18 fewer to 62 more)	⊕⊕⊕O MODERATE	CRITICAL
Drug resistance - 96 weeks												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/320 (2.2%)	10/441 (2.3%)	RR 1.13 (0.43 to 2.96)	3 more per 1000 (from 13 fewer to 44 more)	⊕⊕⊕O	CRITICAL

								2.3%		3 more per 1000 (from 13 fewer to 45 more)	MODERATE	
Serious adverse event - 48 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	27/282 (9.6%)	28/281 (10%) 10%	RR 0.96 (0.58 to 1.59)	4 fewer per 1000 (from 42 fewer to 59 more) 4 fewer per 1000 (from 42 fewer to 59 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse event - 96 weeks												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	37/320 (11.6%)	56/441 (12.7%) 12.1%	RR 0.84 (0.56 to 1.25)	20 fewer per 1000 (from 56 fewer to 32 more) 19 fewer per 1000 (from 53 fewer to 30 more)	⊕⊕⊕O MODERATE	CRITICAL
Grade 3 or 4 AST elevation - 48 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/282 (1.8%)	6/281 (2.1%) 2.1%	RR 0.83 (0.26 to 2.69)	4 fewer per 1000 (from 16 fewer to 36 more) 4 fewer per 1000 (from 16 fewer to 35 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Grade 3 or 4 AST elevation - 96 weeks												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/317 (2.8%)	13/441 (2.9%) 2.9%	RR 0.92 (0.39 to 2.17)	2 fewer per 1000 (from 18 fewer to 34 more) 2 fewer per 1000 (from 18 fewer to 34 more)	⊕⊕⊕O MODERATE	CRITICAL
Grade 3 or 4 ALT elevation - 48 weeks												
1	randomised	no serious	no serious	no serious	no serious	none	6/282 (2.1%)	5/281	RR 1.2 (0.37 to	4 more per 1000 (from 11	⊕⊕⊕⊕	CRITICAL

	trials	limitations	inconsistency	indirectness	imprecision			(1.8%) 1.8%	3.87)	fewer to 51 more) 4 more per 1000 (from 11 fewer to 52 more)	HIGH	
Grade 3 or 4 ALT elevation - 96 weeks												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/317 (2.8%)	7/441 (1.6%) 1.5%	RR 1.87 (0.7 to 4.97)	14 more per 1000 (from 5 fewer to 63 more) 13 more per 1000 (from 5 fewer to 60 more)	⊕⊕⊕O MODERATE	CRITICAL
Grade 3 or 4 total cholesterol - 96 weeks												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/305 (4.3%)	0/436 (0%) 0%	RR 22.25 (2.83 to 175.02)	0 more per 1000 (from 0 more to 0 more) 0 more per 1000 (from 0 more to 0 more)	⊕⊕OO LOW	NOT IMPORTANT
Grade 3 or 4 LDL cholesterol - 48 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/280 (3.6%)	3/281 (1.1%) 1.1%	RR 3.35 (0.93 to 12.03)	25 more per 1000 (from 1 fewer to 118 more) 26 more per 1000 (from 1 fewer to 121 more)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Grade 3 or 4 LDL cholesterol - 96 weeks												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/301 (6.3%)	4/431 (0.9%) 0.9%	RR 6.3 (2.14 to 18.59)	49 more per 1000 (from 11 more to 163 more) 48 more per 1000 (from 10 more to 158 more)	⊕⊕⊕O MODERATE	NOT IMPORTANT
Grade 3 or 4 triglycerides - 48 weeks												

1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	3/282 (1.1%)	1/281 (0.4%) 0.4%	RR 2.99 (0.31 to 28.57)	7 more per 1000 (from 2 fewer to 98 more) 8 more per 1000 (from 3 fewer to 110 more)		NOT IMPORTANT
Grade 3 or 4 triglycerides - 96 weeks												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/305 (2.3%)	1/436 (0.2%) 0.2%	RR 8.43 (1.34 to 52.85)	17 more per 1000 (from 1 more to 119 more) 15 more per 1000 (from 1 more to 104 more)	⊕⊕OO LOW	NOT IMPORTANT
Lipoatrophy (loss of 20% or more appendicular fat) - 96 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/38 (5.3%)	3/37 (8.1%) 8.1%	RR 0.65 (0.11 to 3.67)	28 fewer per 1000 (from 72 fewer to 216 more) 28 fewer per 1000 (from 72 fewer to 216 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Discontinued due to adverse events - 48 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/282 (6%)	9/281 (3.2%) 3.2%	RR 1.88 (0.85 to 4.15)	28 more per 1000 (from 5 fewer to 101 more) 28 more per 1000 (from 5 fewer to 101 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Discontinued due to adverse events - 96 weeks												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/320 (5.6%)	13/441 (2.9%) 2.6%	RR 1.58 (0.78 to 3.21)	17 more per 1000 (from 6 fewer to 65 more) 15 more per 1000 (from 6 fewer to 57 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] Randomisation and allocation concealment not stated in one study
[2] Wide confidence intervals

D Darunavir versus lopinavir

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Darunavir versus lopinavir	control	Relative (95% CI)	Absolute		
Viral suppression <50 copies/mL - 48 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	286/340 (84.1%)	270/346 (78%) 78%	RR 1.08 (1 to 1.16)	62 more per 1000 (from 0 more to 125 more) 62 more per 1000 (from 0 more to 125 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Viral suppression <50 copies/mL - 96 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	271/343 (79%)	246/346 (71.1%) 71.1%	RR 1.11 (1.02 to 1.21)	78 more per 1000 (from 14 more to 149 more) 78 more per 1000 (from 14 more to 149 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Virological failure - 48 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	34/340 (10%)	49/346 (14.2%) 14.2%	RR 0.71 (0.47 to 1.07)	41 fewer per 1000 (from 75 fewer to 10 more) 41 fewer per 1000 (from 75 fewer to 10 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Virological failure - 96 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	41/343 (12%)	59/346 (17.1%) 17.1%	RR 0.7 (0.48 to 1.01)	51 fewer per 1000 (from 89 fewer to 2 more) 51 fewer per 1000 (from 89 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Drug resistance - 48 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	1/340 (0.3%)	3/346 (0.9%) 0.9%	RR 0.34 (0.04 to 3.24)	6 fewer per 1000 (from 8 fewer to 19 more) 6 fewer per 1000 (from 9 fewer to 20 more)	⊕⊕⊕O MODERATE	CRITICAL
Drug resistance - 96 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/343 (1.7%)	12/346 (3.5%) 3.5%	RR 0.5 (0.19 to 1.33)	17 fewer per 1000 (from 28 fewer to 11 more) 18 fewer per 1000 (from 28 fewer to 12 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse event - 48 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	25/343 (7.3%)	41/346 (11.8%) 11.9%	RR 0.62 (0.38 to 0.99)	45 fewer per 1000 (from 1 fewer to 73 fewer) 45 fewer per 1000 (from 1 fewer to 74 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse event - 96 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	34/343 (9.9%)	55/346 (15.9%) 15.9%	RR 0.62 (0.42 to 0.93)	60 fewer per 1000 (from 11 fewer to 92 fewer) 60 fewer per 1000 (from 11	⊕⊕⊕⊕ HIGH	CRITICAL

										fewer to 92 fewer)		
Grade 3 or 4 adverse event - 48 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	64/343 (18.7%)	75/346 (21.7%) 21.7%	RR 0.86 (0.64 to 1.16)	30 fewer per 1000 (from 78 fewer to 35 more) 30 fewer per 1000 (from 78 fewer to 35 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Discontinuation due to adverse event - 48 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/343 (3.5%)	24/346 (6.9%) 6.9%	RR 0.5 (0.26 to 0.99)	35 fewer per 1000 (from 1 fewer to 51 fewer) 34 fewer per 1000 (from 1 fewer to 51 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Discontinuation due to adverse event - 96 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/343 (5.5%)	35/346 (10.1%) 10.1%	RR 0.55 (0.32 to 0.94)	46 fewer per 1000 (from 6 fewer to 69 fewer) 45 fewer per 1000 (from 6 fewer to 69 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] Wide confidence intervals

D Efavirenz vs lopinavir sensitivity analysis without Sierra-Madero

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Efavirenz	lopinavir sensitivity analysis without Sierra-Madero	Relative (95% CI)	Absolute		
Viral suppression < 50 copies/mL - 48 weeks												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/63 (57.1%)	40/63 (63.5%) 63.5%	RR 0.9 (0.68 to 1.2)	63 fewer per 1000 (from 203 fewer to 127 more) 64 fewer per 1000 (from 203 fewer to 127 more)	⊕⊕OO LOW	CRITICAL
Viral suppression < 50 copies/mL - 96 weeks												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	223/250 (89.2%)	195/253 (77.1%) 77.1%	RR 1.16 (1.07 to 1.25)	123 more per 1000 (from 54 more to 193 more) 123 more per 1000 (from 54 more to 193 more)	⊕⊕OO LOW	CRITICAL
Virological failure - 48 weeks												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	1/63 (1.6%)	1/63 (1.6%) 1.6%	RR 1 (0.06 to 15.64)	0 fewer per 1000 (from 15 fewer to 232 more) 0 fewer per 1000 (from 15 fewer to 234 more)	⊕OOO VERY LOW	CRITICAL
Virological failure - 96 weeks												
1	randomised	very	no serious	no serious	no serious	none	60/250	94/253 (37.2%)	RR 0.65 (0.49	130 fewer per 1000 (from	⊕⊕OO	CRITICAL

	trials	serious[1,2]	inconsistency	indirectness	imprecision		(24%)	37.2%	to 0.85)	56 fewer to 189 fewer) 130 fewer per 1000 (from 56 fewer to 190 fewer)	LOW	
Drug resistance - 48 weeks												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	1/63 (1.6%)	1/63 (1.6%) 1.6%	RR 1 (0.06 to 15.64)	0 fewer per 1000 (from 15 fewer to 232 more) 0 fewer per 1000 (from 15 fewer to 234 more)	⊕OOO VERY LOW	CRITICAL
Drug resistance - 96 weeks												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/250 (8.8%)	16/253 (6.3%) 6.3%	RR 1.39 (0.75 to 2.59)	25 more per 1000 (from 16 fewer to 101 more) 25 more per 1000 (from 16 fewer to 100 more)	⊕⊕OO LOW	CRITICAL
CD4 cell count (follow-up 48 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	63	63	-	MD 51 higher (33.51 lower to 135.51 higher)	⊕OOO VERY LOW	IMPORTANT
Grade 3 or 4 clinical adverse event - 48 weeks												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/63 (6.3%)	2/63 (3.2%) 3.2%	RR 2 (0.38 to 10.53)	32 more per 1000 (from 20 fewer to 303 more) 32 more per 1000 (from 20 fewer to 305 more)	⊕⊕OO LOW	CRITICAL
Grade 3 or 4 clinical adverse event - 96 weeks												
1	randomised	very	no serious	no serious	no serious	none	42/250	46/253 (18.2%)	RR 0.92 (0.63	15 fewer per 1000 (from	⊕⊕OO	CRITICAL

	trials	serious[1,2]	inconsistency	indirectness	imprecision		(16.8%)	18.2%	to 1.35)	67 fewer to 64 more) 15 fewer per 1000 (from 67 fewer to 64 more)	LOW	
Grade 3 or 4 diarrhoea - 96 weeks												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	1/250 (0.4%)	8/253 (3.2%) 3.2%	RR 0.13 (0.02 to 1)	28 fewer per 1000 (from 31 fewer to 0 more) 28 fewer per 1000 (from 31 fewer to 0 more)	⊕OOO VERY LOW	IMPORTANT
Grade 3 or 4 rash - 96 weeks												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	6/250 (2.4%)	2/253 (0.8%) 0.8%	RR 3.04 (0.62 to 14.9)	16 more per 1000 (from 3 fewer to 110 more) 16 more per 1000 (from 3 fewer to 111 more)	⊕OOO VERY LOW	CRITICAL
Grade 3 or 4 laboratory adverse event - 96 weeks												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	72/250 (28.8%)	80/253 (31.6%) 31.6%	RR 0.91 (0.7 to 1.19)	28 fewer per 1000 (from 95 fewer to 60 more) 28 fewer per 1000 (from 95 fewer to 60 more)	⊕⊕OO LOW	IMPORTANT
Total cholesterol (follow-up 48 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	63	63	-	MD 12 higher (1.3 lower to 25.3 higher)	⊕⊕OO LOW	NOT IMPORTANT
Grade 3 or 4 LDL cholesterol - 96 weeks												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	7/250 (2.8%)	2/253 (0.8%)	RR 3.54 (0.74 to 16.88)	20 more per 1000 (from 2 fewer to 126 more)	⊕OOO VERY	NOT IMPORTANT

								0.8%		20 more per 1000 (from 2 fewer to 127 more)	LOW	
Grade 3 or 4 triglycerides - 96 weeks												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/250 (2.4%)	16/253 (6.3%) 6.3%	RR 0.38 (0.15 to 0.95)	39 fewer per 1000 (from 3 fewer to 54 fewer) 39 fewer per 1000 (from 3 fewer to 54 fewer)	⊕⊕OO LOW	NOT IMPORTANT
Grade 3 or 4 AST or ALT - 96 weeks												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/250 (4%)	16/253 (6.3%) 6.3%	RR 0.63 (0.29 to 1.37)	23 fewer per 1000 (from 45 fewer to 23 more) 23 fewer per 1000 (from 45 fewer to 23 more)	⊕⊕OO LOW	CRITICAL
Lipodystrophy - 48 weeks												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	0/63 (0%)	1/63 (1.6%) 1.6%	RR 0.33 (0.01 to 8.03)	11 fewer per 1000 (from 16 fewer to 112 more) 11 fewer per 1000 (from 16 fewer to 112 more)	⊕OOO VERY LOW	IMPORTANT
Lipodystrophy - 96 weeks												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/250 (3.2%)	3/253 (1.2%) 1.2%	RR 2.7 (0.72 to 10.06)	20 more per 1000 (from 3 fewer to 107 more) 20 more per 1000 (from 3 fewer to 109 more)	⊕⊕OO LOW	IMPORTANT

[1] Randomisation and/or allocation concealment not stated
[2] Large drop-out
[3] Wide confidence intervals