Combined file for "which 3rd agent?"

Main comparisons:

1 Cobicistat/ atazanavir/ emtricitabine/ tenofovir df versus atazanavir/ ritonavir/emtricitabine/ tenofovir df

2 Darunavir/ritonavir + tenofovir/emtricitabine versus atazanavir + tenofovir/emtricitabine

3 Dolutegravir versus darunavir plus ritonavir, with investigator-selected tenofovir–emtricitabine or abacavir–lamivudine

4 Dolutegravir versus raltegravir, with investigator-selected NRTIs (TDF/FTC or ABC/3TC)

5 Dolutegravir/TDF/FTC versus raltegravir/TDF/FTC; subgroups by baseline viral load

6 Dolutegravir/ABC/3TC versus raltegravir/ABC/3TC; subgroups by baseline viral load

7 Dolutegravir/abacavir/lamivudine versus efavirenz/tenofovir/emtricitabine

8 Efavirenz versus efavirenz-free regimens

9 Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/ emtricitabine/ tenofovir disoproxil fumarate

10 Elvitegravir, cobicistat, emtricitabine, and tenofovir versus ritonavir-boosted atazanavir plus emtricitabine/ tenofovir

11 Raltegravir vs. atazanavir/ritonavir, all with tenofovir/emtricitabine

12 Raltegravir vs. darunavir/ritonavir, all with tenofovir/emtricitabine

Key outcomes:

a) Efficacy HIV RNA <50 copies/mL; subgroups by < or >100,000 copies/mL at baseline

b) Virological failure; subgroups by < or >100,000 copies/mL at baseline

c) Resistance: i) as a proportion of all randomised patients

ii) as a proportion of those with virological failure

d) Discontinuation due to adverse events

e) Grade 3-4 adverse events (clinical)

f) Grade 3-4 adverse events (laboratory)

g) Grade 3-4 rash

h) Grade 3-4 raised AST or ALT

i) Grade 3-4 CNS events

j) Grade 3-4 diarrhoea

NB * by the name of a citation means this is a new paper since the last guidelines (but may be reporting an existing study); ^ means this is a new study altogether.

Evidence tables and Forest plots:

1 Cobicistat/ atazanavir/ emtricitabine/ tenofovir df versus atazanavir/ ritonavir/emtricitabine/ tenofovir df

Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
Richard Elion et al for the GS-US-216–0105 Study Team. Phase 2 study of cobicistat versus ritonavir each with once-daily	RCT: Randomized, partially placebo-controlled, double-blind, multicentre study Randomisation: stratified by screening HIV-1 RNA ≤ or > 100 000 copies/ml; no further details Allocation concealment: Not stated Blinding: Partial Comparable groups at baseline: Baseline	85 randomised; 6 never received treatment	Inclusion: HIV-1-infected adults (≥18 years), screening plasma HIV-1 RNA at least 5000 copies/ml, CD4 cell count more than 50 cells/µl, no prior use of approved or experimental anti-HIV drugs and no nucleoside or non-nucleoside reverse transcriptase inhibitor, or primary protease inhibitor genotypic resistance	Placebo-blinded once-daily cobicistat 150mg with open-label atazanavir and fixed-dose	Placebo-blinded once-daily ritonavir 100mg with open-label atazanavir and fixed-dose	48 weeks	Primary efficacy endpoint was as follows: proportion of participants with HIV-1 RNA less than 50 copies/ml at week 24 using point estimates and 95% confidence interval for difference in response rates by	Probably Gilead Sciences

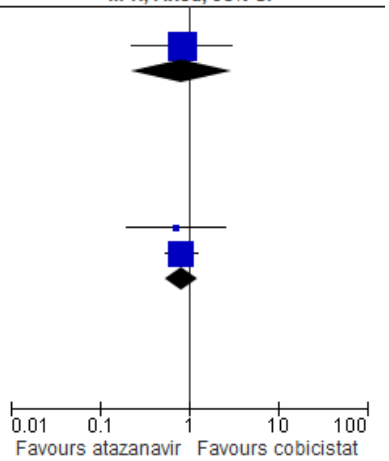
atazanavir and fixed-dose emtricitabine/ tenofovir df in the initial treatment of HIV infection. AIDS 2011; 25: 1881–1886	demographics and disease characteristics were similar between treatment groups. Sample size calculation: Not stated Intention to treat analysis: Yes Drop out: one patient on each treatment was lost to follow-up, one ATV/co participant withdrew consent and another was discontinued at the investigator's discretion due to nonadherence to protocol, and one ATV/r participant had a protocol violation. Setting: The study was conducted in the United States		mutations (International AIDS Society - U.S.A. guidelines), normal ECG, estimated glomerular filtration rate (eGFR, Cockcroft–Gault) at least 80 ml/min, aspartate amino transferase or alanine aminotransferase 2.5 times upper limit of normal or less, total bilirubin 1.5 mg/dl or less, and for women, a negative serum pregnancy test. Exclusion criteria were as follows: hepatitis B or C co-infection, new AIDS-defining condition within 30 days of screening, or vaccination within 90 days of study treatment dosing.	emtricitabine/ tenofovir df (n=50)	emtricitabine/ tenofovir df (n=29)		normal approximation methods, stratified by baseline HIV-1 RNA level. Secondary endpoints were as follows: proportion of participants with HIV-1 RNA of less than 50 copies/ml at week 48, and CD4 + cell count at weeks 24 and 48. Safety and pharmacokinetic endpoints were summarized using descriptive statistics.	
Joel E. Gallant et al. Cobicistat Versus Ritonavir as a Pharmaco-enhancer of Atazanavir Plus Emtricitabine/ Tenofovir Disoproxil Fumarate in Treatment-Naive HIV Type 1–Infected Patients: Week 48 Results.	RCT: randomized, double-blind, double-dummy, active-controlled trial (NCT01108510; Study GS-US-216-0114) Randomisation: A computer-generated allocation sequence that used a block size of 4 was created by Bracket (San Francisco, CA), and randomization was stratified by screening HIV-1 RNA level (≤100 000 copies/mL and >100 000 copies/mL). Allocation concealment: Investigators randomly assigned patients to one of the 2 treatment arms by phone or Internet, using an interactive system (provided and managed by Bracket). Blinding: investigators, patients, and study staff were blinded to the treatment group Comparable groups at baseline: Demographic and general baseline characteristics were similar	698 randomised; 692 treated	Inclusion: Patients (target enrollment, 700) were HIV type 1 (HIV-1)-infected adults at least 18 years old with a plasma HIV-1 RNA level of ≥ 5000 copies/mL and no prior use of antiretroviral agents. An estimated glomerular filtration rate (eGFR) of at least 70 mL/min and sensitivity to ATV, FTC, and TDF by the infecting strain, determined on the basis of HIV-1 genotyping (GeneSeq assay, Monogram Biosciences, South San Francisco, CA), were required at screening. Additional inclusion criteria included aspartate aminotransferase (AST) and alanine aminotransferase (ALT)	Cobicistat once daily plus atazanavir (ATV) in combination with emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) (n=344)	Ritonavir once daily plus atazanavir (ATV) in combination with emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) (n=348)	48 weeks	The primary analysis included all clinical, laboratory, and virologic data available after the last patient had completed the week 48 study visit or prematurely discontinued receipt of the study drug. The primary end point was the proportion of patients with virologic suppression (HIV–1 RNA load, <50 copies/mL) at week 48, in accordance	Gilead Sciences.

The Journal of Infectious Diseases 2013; 208: 32–9	between the 2 treatment groups. Sample size calculation: A sample size of 700 patients provided at least 95% power to establish noninferiority with respect to the percentage of patients achieving virologic success at week 48, as defined by the FDA snapshot analysis, between the 2 treatment groups. This assumes response rates of 79.5% in both treatment groups, a noninferiority margin of 12%, and a significance level of the test at a 1-sided, 0.025 level. Intention to treat analysis: Yes Drop out: 37/692 (5%) were lost to follow up, non-compliant, withdrew consent, withdrew at investigator's discretion, became pregnant or had protocol violation Setting: International		levels of ≤5 times upper limit of normal, a total bilirubin level of ≤1.5 mg/dL or a normal direct bilirubin level, an absolute neutrophil count of ≥1000 cells/mm3, a platelet count of ≥50 000 platelets/mm3, a haemoglobin level of ≥8.5 g/dL, and a negative result of a serum pregnancy test (if applicable). Positivity for hepatitis B virus surface antigen or hepatitis C virus antibody was allowed. There was no screening CD4+ T-cell count requirement. Exclusion: patients with new AIDS-defining conditions or serious infections within 30 days of screening				with the US Food and Drug Administration (FDA)–defined snapshot analysis; the intention-to-treat (ITT) population was used to assess the noninferiority of COBI treatment, compared with RTV treatment, using a conventional 95% confidence interval (CI) approach with a prespecified noninferiority margin of 12%.	

Forest plot of comparison: 1 Cobicistat/ atazanavir/ emtricitabine/ tenofovir df versus atazanavir/ ritonavir/ emtricitabine/ tenofovir df, outcome: 1.1 HIV RNA <50 copies/mL.

Study or Subgroup	Cobicistat/ atazanavir/ emtricitabine/ tenofovir df Events	Total	Atazanavir/ ritonavir/ emtricitabine/ tenofovir df Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Week 24						
Elion11 GS-US-216-0105*^	42	50	25	29	100.0%	0.84 [0.23, 3.08]
Subtotal (95% CI)		**50**		**29**	**100.0%**	**0.84 [0.23, 3.08]**
Total events	42		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.79)						
1.1.2 Week 48						
Elion11 GS-US-216-0105*^	41	50	25	29	11.3%	0.73 [0.20, 2.62]
Gallant 2013: Study 114*^	293	344	304	348	88.7%	0.83 [0.54, 1.28]
Subtotal (95% CI)		**394**		**377**	**100.0%**	**0.82 [0.54, 1.24]**
Total events	334		329			
Heterogeneity: $Chi^2 = 0.04$, df = 1 (P = 0.85); $I^2 = 0\%$						
Test for overall effect: Z = 0.95 (P = 0.34)						

Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.97), $I^2 = 0\%$

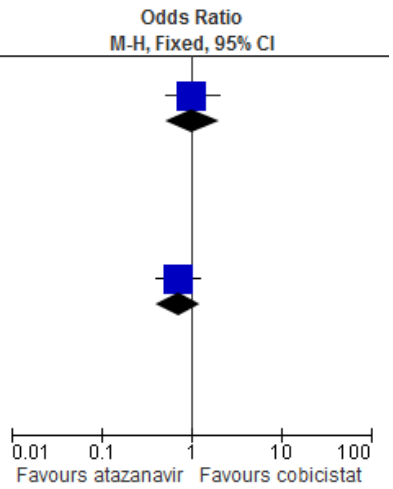


Elion 2011 did not report results by baseline HIV RNA ≤ or >100 000 copies/ml, although randomisation was stratified on this variable.

1 Cobicistat/ atazanavir/ emtricitabine/ tenofovir df versus atazanavir/ ritonavir/ emtricitabine/ tenofovir df, outcome: 1.2 HIV RNA <50 copies/mL; subgroups.

Study or Subgroup	Cobicistat/ atazanavir/ emtricitabine/ tenofovir df Events	Total	Atazanavir/ ritonavir/ emtricitabine/ tenofovir df Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Week 48; >100,000 at baseline						
Gallant 2013: Study 114*^	114	132	123	143	100.0%	1.03 [0.52, 2.04]
Subtotal (95% CI)		**132**		**143**	**100.0%**	**1.03 [0.52, 2.04]**
Total events	114		123			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.93)						
1.2.2 Week 48; <100,000 at baseline						
Gallant 2013: Study 114*^	179	212	181	205	100.0%	0.72 [0.41, 1.27]
Subtotal (95% CI)		**212**		**205**	**100.0%**	**0.72 [0.41, 1.27]**
Total events	179		181			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.14 (P = 0.25)						

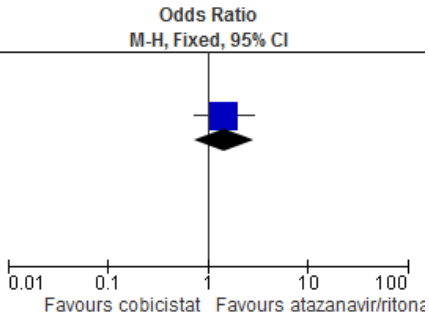
Test for subgroup differences: Chi² = 0.63, df = 1 (P = 0.43), I² = 0%



Forest plot of comparison: 1 Cobicistat/ atazanavir/ emtricitabine/ tenofovir df versus atazanavir/ ritonavir/ emtricitabine/ tenofovir df, outcome: 1.3 Virological failure.

Study or Subgroup	Cobicistat/ atazanavir/ emtricitabine/ tenofovir df Events	Total	Atazanavir/ ritonavir/ emtricitabine/ tenofovir df Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.3.1 Week 48						
Elion11 GS-US-216-0105*^	0	50	0	29		Not estimable
Gallant 2013: Study 114*^	20	344	14	348	100.0%	1.47 [0.73, 2.97]
Subtotal (95% CI)		**394**		**377**	**100.0%**	**1.47 [0.73, 2.97]**
Total events	20		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						

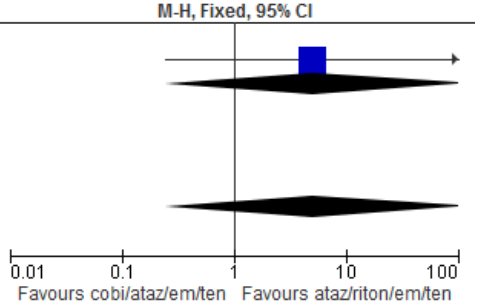
Test for subgroup differences: Not applicable



Neither Elion 2011 nor Gallant 2013 reported virological failure by baseline RNA load < or > 100,000 copies/mL.

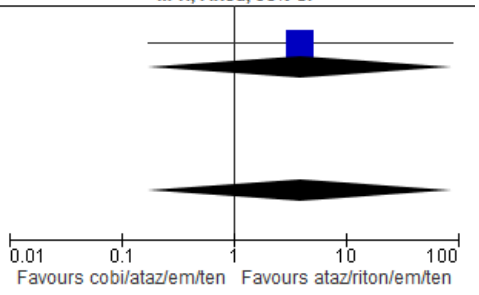
Forest plot of comparison: 1 Cobicistat/ atazanavir/ emtricitabine/ tenofovir df versus atazanavir/ ritonavir/ emtricitabine/ tenofovir df, outcome: 1.4 Resistance (% of total participants).

	Cobicistat/ atazanavir/ emtricitabine/ tenofovir df		Atazanavir/ ritonavir/ emtricitabine/ tenofovir df			Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
1.4.1 Week 48						
Gallant 2013: Study 114*^	2	344	0	348	100.0%	5.09 [0.24, 106.36]
Subtotal (95% CI)		**344**		**348**	**100.0%**	**5.09 [0.24, 106.36]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
Total (95% CI)		**344**		**348**	**100.0%**	**5.09 [0.24, 106.36]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
Test for subgroup differences: Not applicable						



Forest plot of comparison: 1 Cobicistat/ atazanavir/ emtricitabine/ tenofovir df versus atazanavir/ ritonavir/ emtricitabine/ tenofovir df, outcome: 1.5 Resistance (% of virological failures).

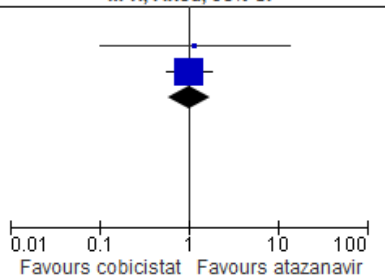
	Cobicistat/ atazanavir/ emtricitabine/ tenofovir df		Atazanavir/ ritonavir/ emtricitabine/ tenofovir df			Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
1.5.1 Week 48						
Gallant 2013: Study 114*^	2	20	0	14	100.0%	3.92 [0.17, 88.15]
Subtotal (95% CI)		**20**		**14**	**100.0%**	**3.92 [0.17, 88.15]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
Total (95% CI)		**20**		**14**	**100.0%**	**3.92 [0.17, 88.15]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
Test for subgroup differences: Not applicable						



Of the 692 randomly assigned and treated patients, 24 (3.5%) met criteria for resistance testing, with 12 of 344 (3.5%) in the COBI group and 12 of 348 (3.4%) in the RTV group. Of the 10 patients in the COBI group with available data, none developed resistance mutations to PIs or TDF; 2 developed resistance mutations to FTC (M184V). Of the 12 patients in the RTV group, none developed resistance mutations.

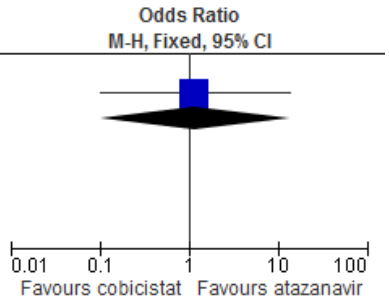
Forest plot of comparison: 1 Cobicistat/ atazanavir/ emtricitabine/ tenofovir df versus atazanavir/ ritonavir/ emtricitabine/ tenofovir df, outcome: 1.6 Discontinued due to adverse event related to study treatment.

	Cobicistat/ atazanavir/ emtricitabine/ tenofovir df		Atazanavir/ ritonavir/ emtricitabine/ tenofovir df			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
1.6.1 Week 48						
Elion11 GS-US-216-0105*^	2	50	1	29	5.0%	1.17 [0.10, 13.46]
Gallant 2013: Study 114*^	25	344	25	348	95.0%	1.01 [0.57, 1.80]
Subtotal (95% CI)		**394**		**377**	**100.0%**	**1.02 [0.58, 1.79]**
Total events	27		26			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.07 (P = 0.94)						
Test for subgroup differences: Not applicable						



Forest plot of comparison: 1 Cobicistat/ atazanavir/ emtricitabine/ tenofovir df versus atazanavir/ ritonavir/ emtricitabine/ tenofovir df, outcome: 1.7 Serious adverse event (clinical).

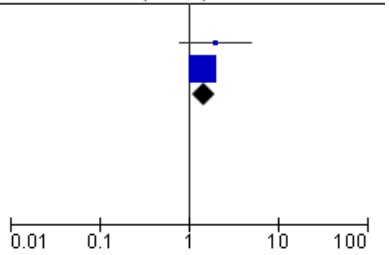
	Cobicistat/ atazanavir/ emtricitabine/ tenofovir df		Atazanavir/ ritonavir/ emtricitabine/ tenofovir df			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
1.7.1 Week 48						
Elion11 GS-US-216-0105*^	2	50	1	29	100.0%	1.17 [0.10, 13.46]
Subtotal (95% CI)		**50**		**29**	**100.0%**	**1.17 [0.10, 13.46]**
Total events	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.12 (P = 0.90)						
Test for subgroup differences: Not applicable						



Forest plot of comparison: 1 Cobicistat/ atazanavir/ emtricitabine/ tenofovir df versus atazanavir/ ritonavir/ emtricitabine/ tenofovir df, outcome: 1.8 Grade 3-4 hyperbilirubinemia.

	Cobicistat/ atazanavir/ emtricitabine/ tenofovir df		Atazanavir/ ritonavir/ emtricitabine/ tenofovir df			Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
1.8.1 Week 48						
Elion11 GS-US-216-0105*^	31	50	13	29	8.4%	2.01 [0.79, 5.08]
Gallant 2013: Study 114*^	225	344	197	348	91.6%	1.45 [1.07, 1.97]
Subtotal (95% CI)		**394**		**377**	**100.0%**	**1.50 [1.12, 2.00]**
Total events	256		210			
Heterogeneity: Chi² = 0.43, df = 1 (P = 0.51); I² = 0%						
Test for overall effect: Z = 2.71 (P = 0.007)						

Odds Ratio M-H, Fixed, 95% CI

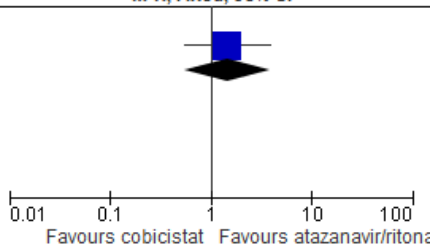


Test for subgroup differences: Not applicable

Forest plot of comparison: 1 Cobicistat/ atazanavir/ emtricitabine/ tenofovir df versus atazanavir/ ritonavir/ emtricitabine/ tenofovir df, outcome: 1.9 Grade 3-4 raised aspartate aminotransferase.

	Cobicistat/ atazanavir/ emtricitabine/ tenofovir df		Atazanavir/ ritonavir/ emtricitabine/ tenofovir df			Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
1.9.1 Week 48						
Gallant 2013: Study 114*^	10	344	7	348	100.0%	1.46 [0.55, 3.88]
Subtotal (95% CI)		**344**		**348**	**100.0%**	**1.46 [0.55, 3.88]**
Total events	10		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.76 (P = 0.45)						

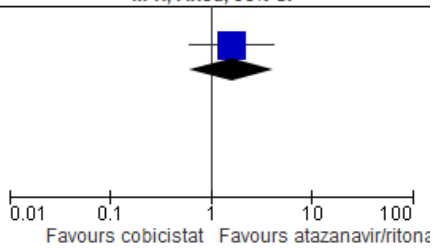
Odds Ratio M-H, Fixed, 95% CI



Test for subgroup differences: Not applicable

Forest plot of comparison: 1 Cobicistat/ atazanavir/ emtricitabine/ tenofovir df versus atazanavir/ ritonavir/ emtricitabine/ tenofovir df, outcome: 1.10 Grade 3-4 raised alanine aminotransferase.

	Cobicistat/ atazanavir/ emtricitabine/ tenofovir df		Atazanavir/ ritonavir/ emtricitabine/ tenofovir df			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.10.1 Week 48							
Gallant 2013: Study 114*^	11	344	7	348	100.0%	1.61 [0.62, 4.20]	
Subtotal (95% CI)		**344**		**348**	**100.0%**	**1.61 [0.62, 4.20]**	
Total events	11		7				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.97 (P = 0.33)							



Test for subgroup differences: Not applicable

No data for Grade 3-4 rash, CNS events or diarrhoea.

2 Darunavir/ritonavir + tenofovir/emtricitabine versus atazanavir + tenofovir/emtricitabine

Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
Judith A. Aberg et al. Metabolic Effects of Darunavir/Ritonavir Versus Atazanavir/ Ritonavir in Treatment-Naive, HIV Type 1-Infected Subjects over 48 Weeks. AIDS Research And Human Retroviruses 2012; 28 (10): 1184-1195.	RCT: phase 4, multicentre, open-label, randomised exploratory study METABOLIK (Metabolic Evaluation in Treatment-naıves Assessing the impact of two Boosted protease inhibitors on LIpids and other marKers) Randomisation: stratified by sex; no further details Allocation concealment: Not stated Blinding: No: open-label Comparable groups at baseline: At baseline, DRV/r subjects had higher mean log 10 baseline viral loads, lower median CD4 + counts, and lower TC and LDL levels compared with ATV/r subjects. Sample size calculation: Assuming a standard deviation (SD) of 75mg/dl for the primary end point and a two-sided 95% confidence interval (CI) with a precision of 42 mg/dl on each side of the estimated difference, it would be required that at least 50 subjects complete the study (25 subjects per treatment arm). To allow for dropouts, an overall sample size of 60 subjects was planned. Intention to treat analysis: Yes Drop out: Of five (14.7%) subjects in the DRV/r arm	65	Inclusion: Eligible subjects were at least 18 years old and naive to ARV therapy (≤10 days' previous ARV therapy at any point) with HIV-1 RNA 1000 copies/ml or higher; there were no CD4 + count restrictions. Subjects were required to have demonstrated sensitivity to DRV, ATV, TDF, and FTC by resistance testing (DRV, ATV, and TDF susceptibility determined by Antivirogram, Virco Lab, Inc., Raritan, NJ; FTC susceptibility determined by virco TYPE HIV-1, Virco Lab, Inc., Raritan, NJ). Exclusion criteria included body mass index greater than 30 kg/m2; fasting glucose greater than 110mg/dl; low-density lipoprotein (LDL) greater than 130mg/dl; triglycerides greater than 200mg/dl; alanine aminotransferase greater than 2.5 times the upper limit of normal; creatinine clearance 50ml/min/m2 or	Darunavir/ ritonavir (DRV/r) 800/100mg once daily with fixed-dose tenofovir/emtricitabine 200/ 300mg (n=34)	Atazanavir /ritonavir (ATV/r) 300/ 100mg once daily with fixed-dose tenofovir/ emtricitabine 200/ 300mg (n=31)	48 weeks	The primary end point was the change in triglyceride levels from baseline to week 12. Secondary end points included week 12 and week 48 changes in other lipid parameters. Additional secondary end points assessed at week 12 and week 48 included changes in glucose and insulin levels, insulin sensitivity (as measured by the homeostasis model assessment of insulin resistance [HOMA-IR] method), inflammatory biomarkers (interleukin [IL]-1 beta, IL-6, tumor necrosis factor receptor II [TNF RII], high sensitivity C-reactive protein [hs-CRP]), coagulation	Janssen Therapeutics.

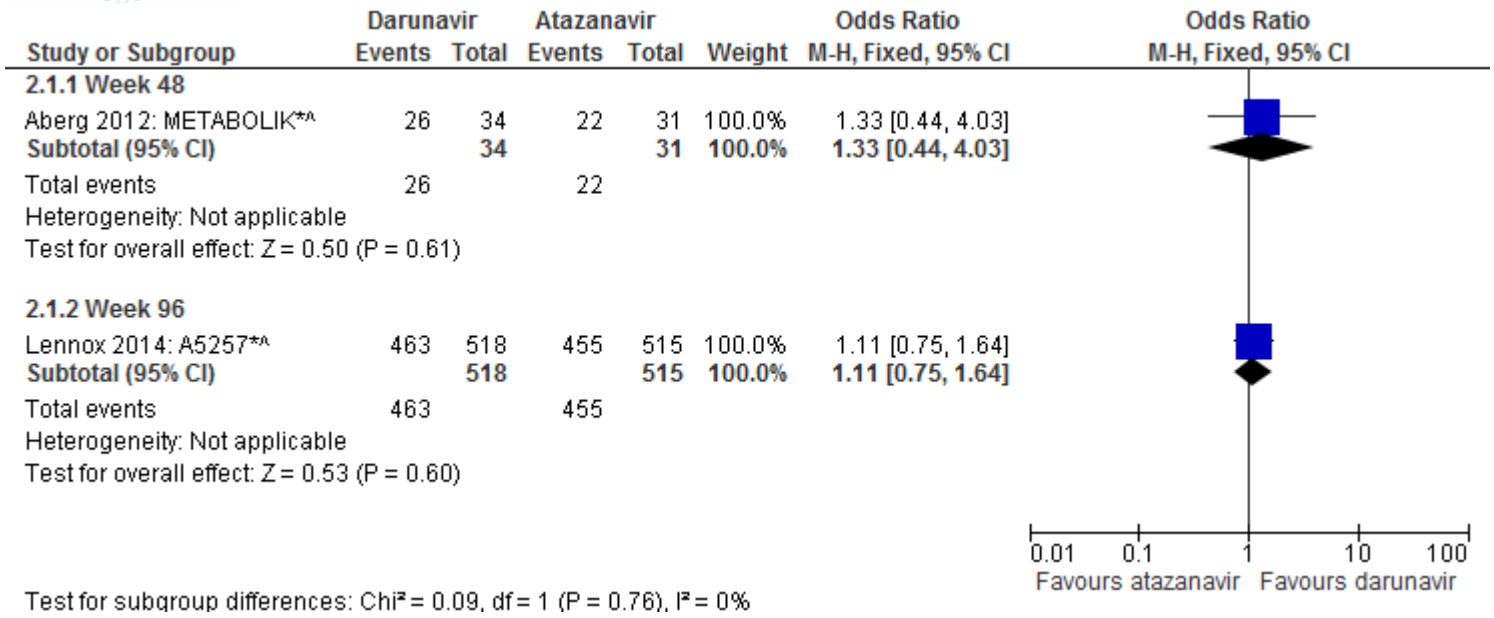
	who discontinued prior to week 48, two withdrew consent, one was noncompliant, one was lost to follow-up, and one relocated. Of six (19.4%) subjects in the ATV/r arm who discontinued early, two discontinued due to AEs (one with grade 3 leukocytoclastic vasculitis and one with grade 1 increased blood creatinine), one discontinued due to pregnancy, one discontinued because of investigational product dispensing error, one was lost to follow-up, and one withdrew consent. Setting: Multi-centre (USA)		lower; evidence of significantly decreased hepatic function or decompensation; presence of any Centers for Disease Control and Prevention active AIDS-defining illness (Category C conditions), except stable cutaneous Kaposi's sarcoma or wasting syndrome; acute or chronic hepatitis A, B, or C; grade 3 or 4 laboratory abnormalities; history of significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances; use of any non-ARV investigational agents within 90 days of screening; receipt of anabolic steroids, atypical antipsychotics, or growth hormones; use of disallowed concomitant therapy; and pregnancy or breastfeeding. Use of lipid-lowering medications, either prescription (e.g., statins or fibrates) or over-the-counter (e.g., fish oil), was prohibited from 28 days before baseline through week 12 of the trial. The use of lipid-lowering medications was allowed after week 12.				biomarkers (fibrinogen, d -dimer), and the microbial translocation biomarker lipopolysaccharide.	
Jeffrey L. Lennox et al for the ACTG	RCT: phase 3, open-label study randomized in a 1:1:1 ratio with follow-up for at least 96 weeks. (ClinicalTrials.gov: NCT00811954)	1809	Inclusion: adults infected with HIV-1 receiving care in the United States and Puerto	Darunavir 800 mg/d, with	Atazanavir 300 mg/d, with	96 weeks	The primary objective was to evaluate regimen	National Institute of Allergy and

A5257 Team. Efficacy and Tolerability of 3 Nonnucleoside e Reverse Transcriptase Inhibitor-Sparing Antiretroviral Regimens for Treatment-Naive Volunteers Infected With HIV-1. A Randomized, Controlled Equivalence Trial. Ann Intern Med. 2014; 161: 461-471. doi:10.7326/M14-1084	Randomisation: permuted blocks stratified according to the HIV-1 RNA level (>100 000 vs. <100 000 copies/mL) with balancing by institution. To ensure treatment balance by cardiovascular risk for an embedded cardiovascular substudy, randomization was stratified by intent to participate in the substudy and 10-year Framingham risk for myocardial infarction or coronary death (<6% vs. >6%). Allocation concealment: Not stated Blinding: No: open label Comparable groups at baseline: Demographic characteristics of the population were well-balanced among the 3 groups Sample size calculation: The target sample size of 600 participants per group would provide 90% power to show equivalence in pairwise regimen comparisons, assuming rates of virologic failure, tolerability failure, and loss to follow-up of 25%, 10%, and 12%, respectively. Intention to treat analysis: Yes Drop out: 13% lost to follow up, or unable to travel to clinic, or non-compliant for other reason Setting: 57 sites in the United States and Puerto Rico		Rico with plasma HIV-1 RNA levels greater than 1000 copies/mL who had received 10 or fewer days of antiretroviral therapy. Participants had documented absence of genotypic resistance to nucleoside reverse transcriptase inhibitors and Pis; integrase genotyping was not required because transmitted integrase resistance is rare. The CD4+ cell count at entry was not limited. Exclusion: Not stated	ritonavir, 100 mg/d, plus combination emtricitabine, 200 mg/d, and tenofovir disoproxil fumarate, 300 mg/d (n=601)	ritonavir, 100 mg/d (n=605); or a third group received raltegravir 400 mg twice daily (n=603), plus combination emtricitabine, 200 mg/d, and tenofovir disoproxil fumarate, 300 mg/d.		equivalence regarding virologic efficacy and tolerability over 96 weeks. Virologic failure was defined as a confirmed HIV-1 RNA level greater than 1000 copies/mL at or after 16 weeks and before 24 weeks from randomization or less than 200 copies/mL at or after 24 weeks. The primary tolerability end point was the time from randomisation to discontinuation of the randomised regimen component for toxicity (per-site attribution); treatment discontinuation for other reasons were considered competing events. Substitution of any component of the fixed-dose combination of TDF plus emtricitabine was not considered tolerability failure. A preplanned composite end	Infectious Diseases.

							point was defined as the earlier occurrence of virologic or tolerability failure. The authors also analyzed the composite U.S. Food and Drug Administration (FDA) end point of time to loss of virologic response (TLOVR), with an HIV-1 RNA failure threshold of 200 copies/mL. Furthermore, they did the FDA snapshot analysis of the proportion of participants receiving randomised treatment with an HIV-1 RNA level less than 30 copies/mL at 96 weeks	
Martinez, E et al on behalf of the ATADAR Team. Metabolic effects of atazanavir/ ritonavir vs darunavir/ ritonavir in combination with	Design: Multicentre, randomized, clinical trial (ATADAR Study, NCT01274780) Randomisation: A random sequence was generated by a computer using blocks of variable size that were balanced at each site, stratifying by total to high-density lipoprotein (HDL) cholesterol ratio < 4.5 or ≥ 4.5. Allocation concealment: Randomization was centralised.	180 randomised	Inclusion: otherwise clinically stable HIV-infected patients aged 18 years or older who had never received any ART and had a plasma HIV RNA ≥1000 copies/mL. A negative urine pregnancy test within 10 days prior to study initiation was also required for participating women of childbearing age.	Darunavir 800 mg (two 400 mg pills)/ ritonavir 100 mg (one pill) plus the fixed-dose combination TDF/ FTC (one pill) once daily	Atazanavir 300 mg (one pill)/ ritonavir 100 mg (one pill) plus the fixed-dose combination TDF/ FTC (one pill) once	96 weeks	The primary endpoint of the ATADAR study was the mean change in total cholesterol at 24 weeks. Secondary endpoints were mean changes in lipids other than total cholesterol (triglycerides, LDL	Supported in part by research grants from Bristol-Myers Squibb and Janssen-Cilag, and Red Temática

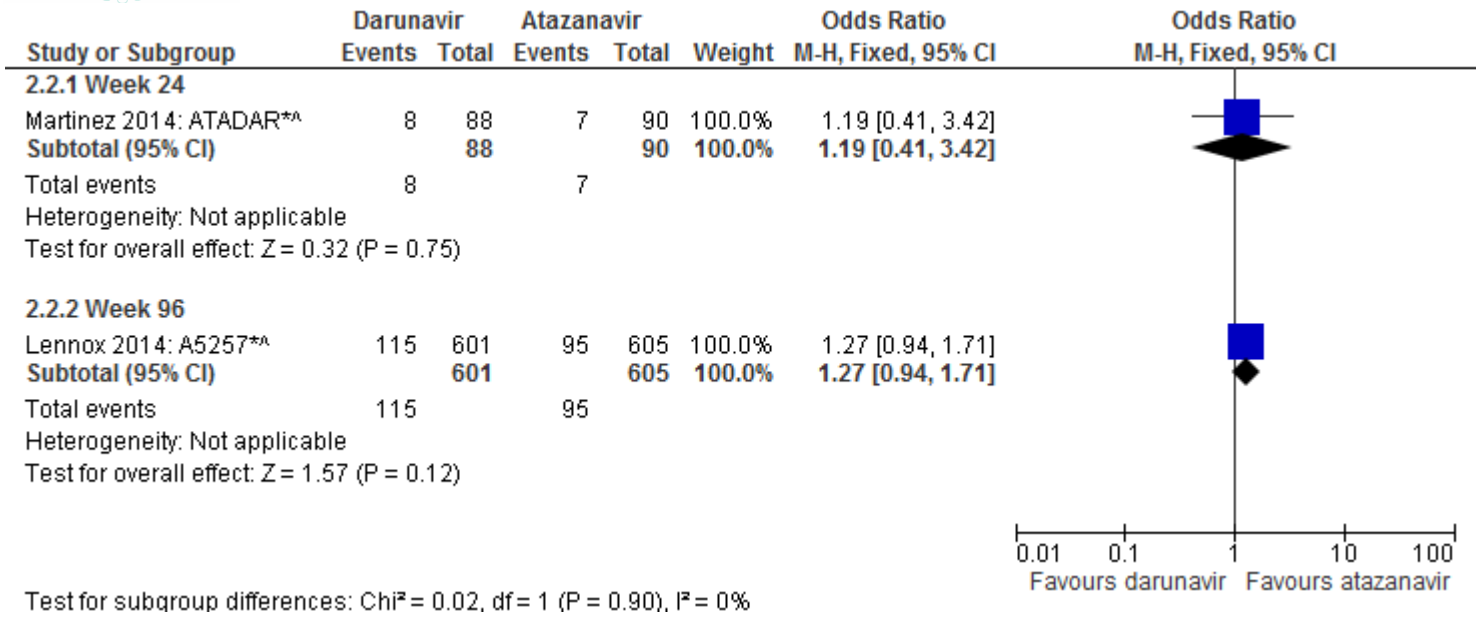
tenofovir/ emtricitabine in anti-retroviral-naïve patients (ATADAR Study). Journal of the International AIDS Society 2012, 15 (Suppl 4): 18202 Martinez, E et al for the ATADAR Study Group. Early lipid changes with atazanavir/ ritonavir or darunavir/ ritonavir. HIV Medicine (2014), 15, 330–338	Blinding: No: open label Comparable groups at baseline: There were no differences in baseline characteristics between the arms. Sample size calculation: Because the difference in total cholesterol change between patients assigned to LPV/r and patients assigned to ATV/r in the CASTLE study was 21 mg/dL, the authors estimated that 75 patients per arm would be needed to detect a difference equal to or higher than that in plasma cholesterol if such a difference between arms exists, with 80% power and 5% bilateral significance. Assuming that up to 15% of patients could be lost to follow-up, the sample size was finally set at 90 patients per arm. Intention to treat analysis: Yes Drop out: 10 protocol violation, lost to follow up or consent withdrawn Setting: 16 centres in Spain		Exclusion criteria were alanine or aspartate amino-transferase ≥ 200 mg/dL (5 times the upper normal limit), creatinine ≥ 2.6 mg/dL (2 times the upper normal limit), diabetes mellitus defined by standard laboratory criteria or by the use of anti-diabetic agents, obesity defined as a body mass index ≥ 30 kg/m2, use of drugs known to affect lipid or glucose metabolism within 1 month prior to inclusion, any AIDS-defining event requiring parenteral therapy, hypersensitivity to or contraindication for any study drug, and pregnancy or lactation at inclusion or expectancy to become pregnant during follow-up.	(n=89)	daily (n=91)		and HDL cholesterol, and total to HDL cholesterol ratio), insulin resistance [measured using homeostatic model assessment (HOMA-IR)], total bilirubin, estimated glomerular filtration rate [calculated using the Modification of Diet in Renal Disease (MDRD) study equation], and CD4 and CD8 cell counts, the proportion of patients with confirmed plasma HIV RNA > 50 copies/mL, and the proportion of patients with study drug discontinuation because of adverse effects.	Cooperativa de Investigación en SIDA G03/173 (RIS-EST11), Ministerio de Sanidad, Servicios Sociales e Igualdad, Spain

Forest plot of comparison: 2 Darunavir/ritonavir + tenofovir/emtricitabine versus atazanavir + tenofovir/emtricitabine, outcome: 2.1 Virological response.



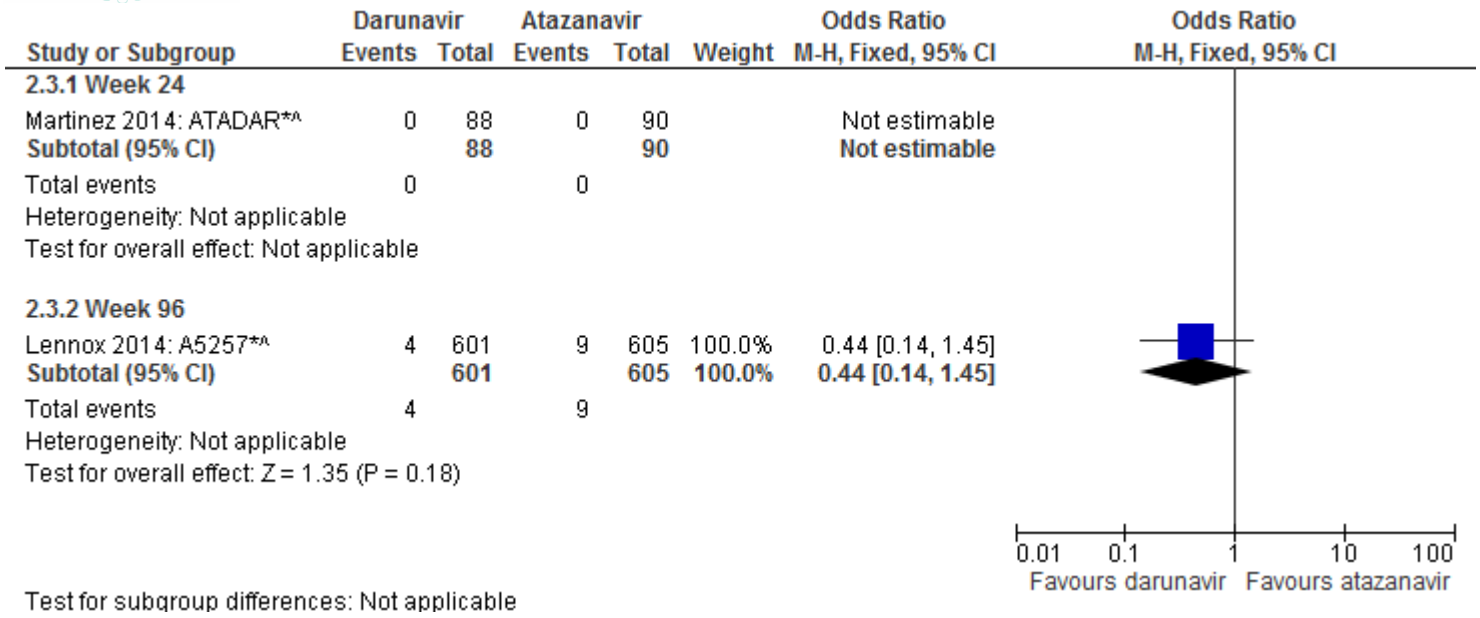
Aberg 2012 and Lennox 2014 did not report response by baseline load < or > 100,000 copies/mL.

Forest plot of comparison: 2 Darunavir/ritonavir + tenofovir/emtricitabine versus atazanavir + tenofovir/emtricitabine, outcome: 2.2 Virological failure.

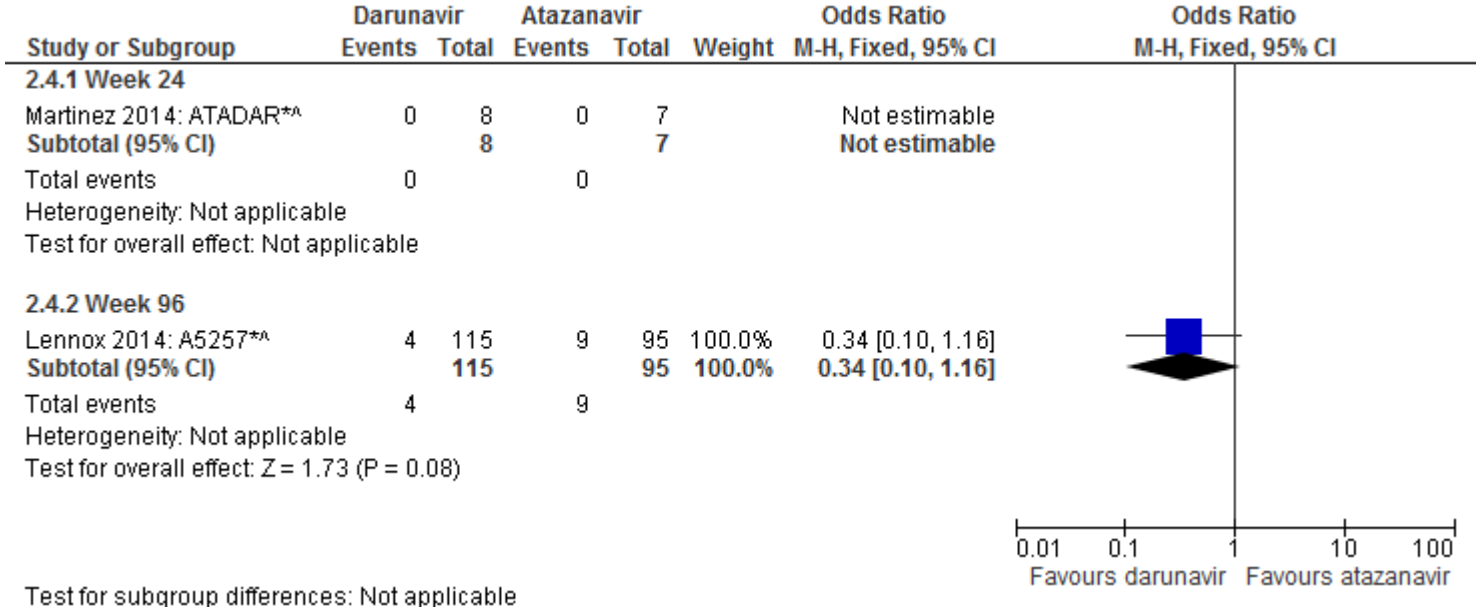


Martinez and Lennox 2014 did not report failure by baseline load < or > 100,000 copies/mL.

Forest plot of comparison: 2 Darunavir/ritonavir + tenofovir/emtricitabine versus atazanavir + tenofovir/emtricitabine, outcome: 2.3 Resistance (% of total patients).



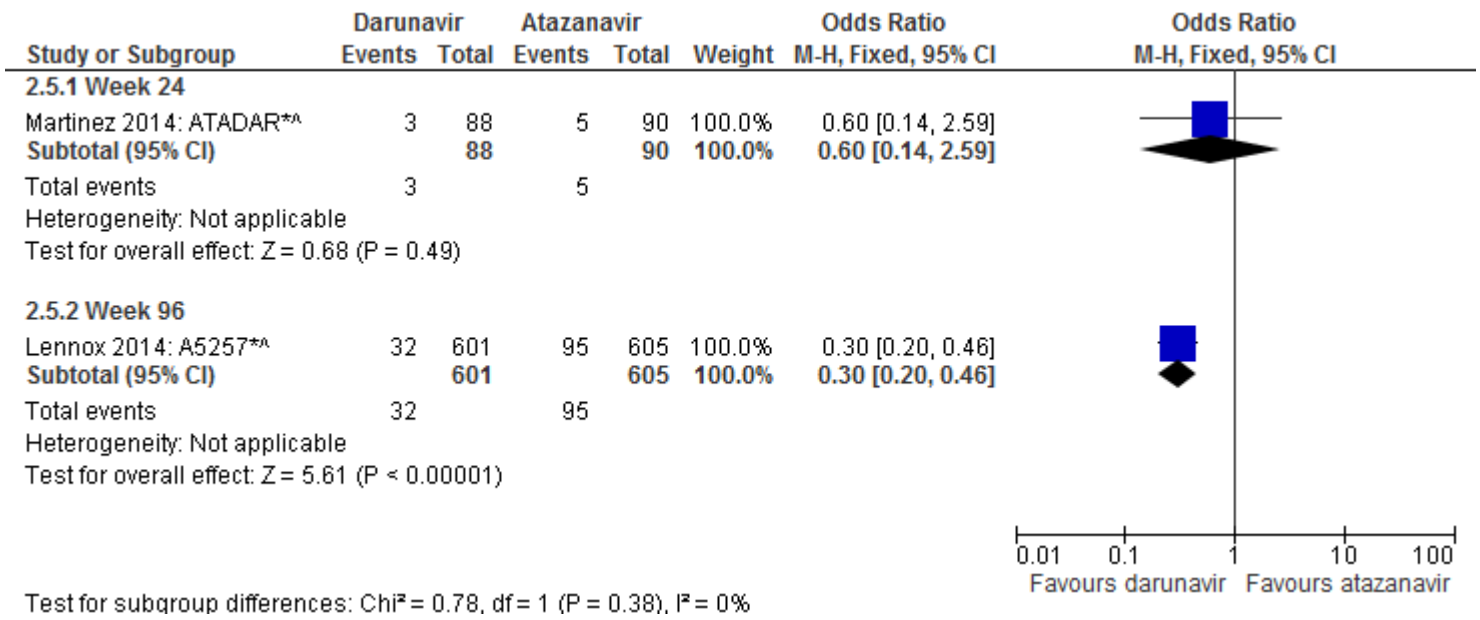
Forest plot of comparison: 2 Darunavir/ritonavir + tenofovir/emtricitabine versus atazanavir + tenofovir/emtricitabine, outcome: 2.4 Resistance (% of patients with virological failure).



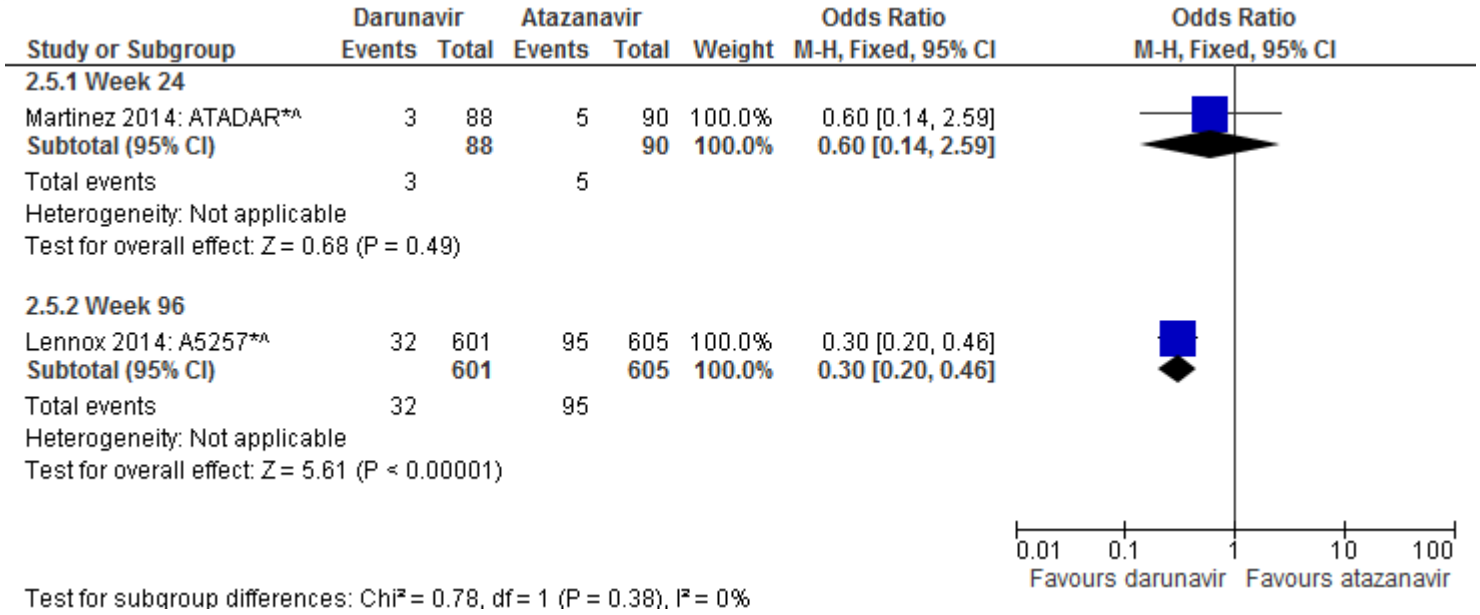
In the ATADAR study (Martinez 2014), seven patients (7.8%) in the ATV/r arm and eight patients (9.1%) in the DRV/r arm had confirmed HIV RNA > 50 copies/mL at 24 weeks (P = 0.79), with values ranging from 52 to 6911 copies/mL. Baseline plasma HIV RNA was significantly higher in patients who showed detectable viral load at 24 weeks [n = 15; mean (SD) viral load 5.59 (0.69) log copies/mL] than in those whose viral load at 24 weeks was below the detection level [n = 163; mean (SD) viral load 4.72 (0.70) log copies/mL] (P < 0.01). Two patients in the ATV/r arm and four patients in the DRV/r arm with confirmed HIV RNA > 50 copies/mL at 24 weeks had genotypic resistance tests performed at that time. HIV RNA could not be amplified in one patient, showed no resistance mutations in four patients, and showed two protease mutations (35G and 63P) not associated with resistance in one patient. No patient with confirmed HIV RNA > 50 copies/mL at 24 weeks had his/her therapy changed for this reason.

In the ACTG A5257 study (Lennox 2014), overall, virologic failure with resistance occurred in 3.0% of study participants randomly assigned to raltegravir (2 of whom developed intermediate-level resistance to dolutegravir) and in 1.5% or fewer of those in either boosted PI group. Twenty-seven participants randomly assigned to a ritonavir-boosted PI regimen who experienced virologic failure had integrase genotyping. Two participants had evidence of treatment-emergent raltegravir resistance despite the absence of known exposure to an integrase inhibitor.

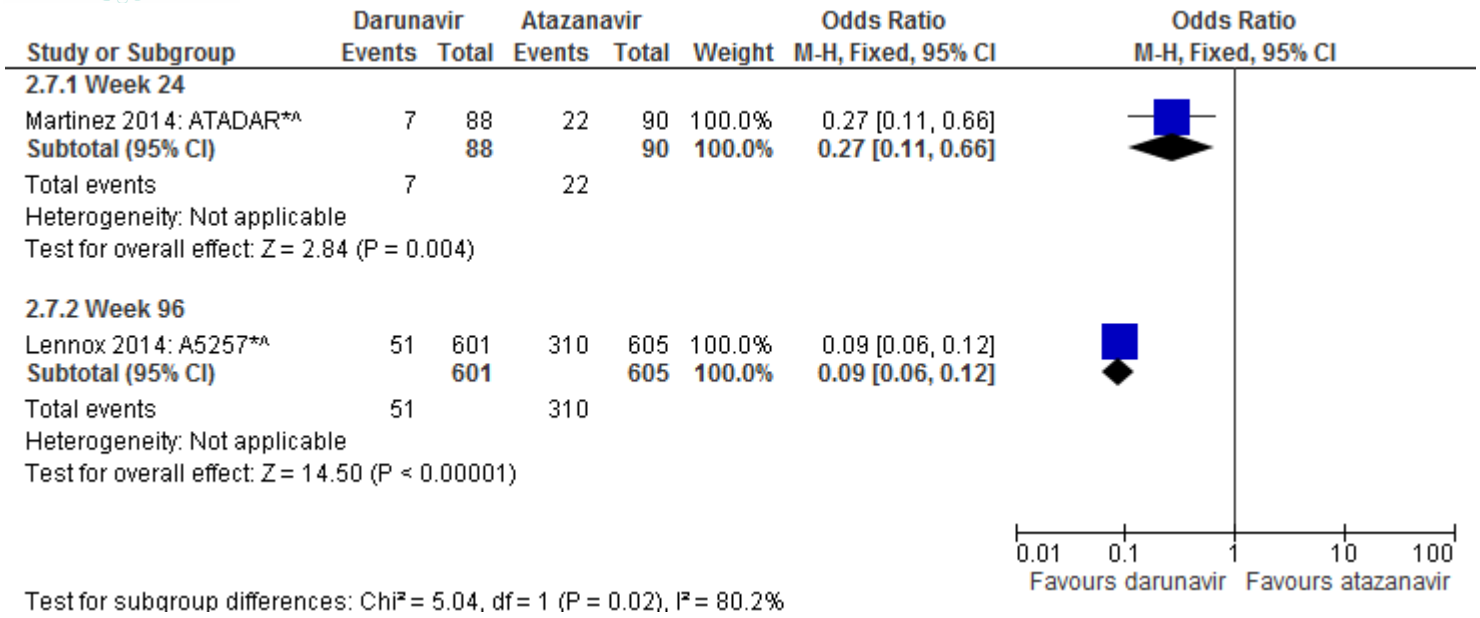
Forest plot of comparison: 2 Darunavir/ritonavir + tenofovir/emtricitabine versus atazanavir + tenofovir/emtricitabine, outcome: 2.5 Discontinued due to adverse events.



Forest plot of comparison: 2 Darunavir/ritonavir + tenofovir/emtricitabine versus atazanavir + tenofovir/emtricitabine, outcome: 2.6 Grade 3-4 adverse events (clinical).

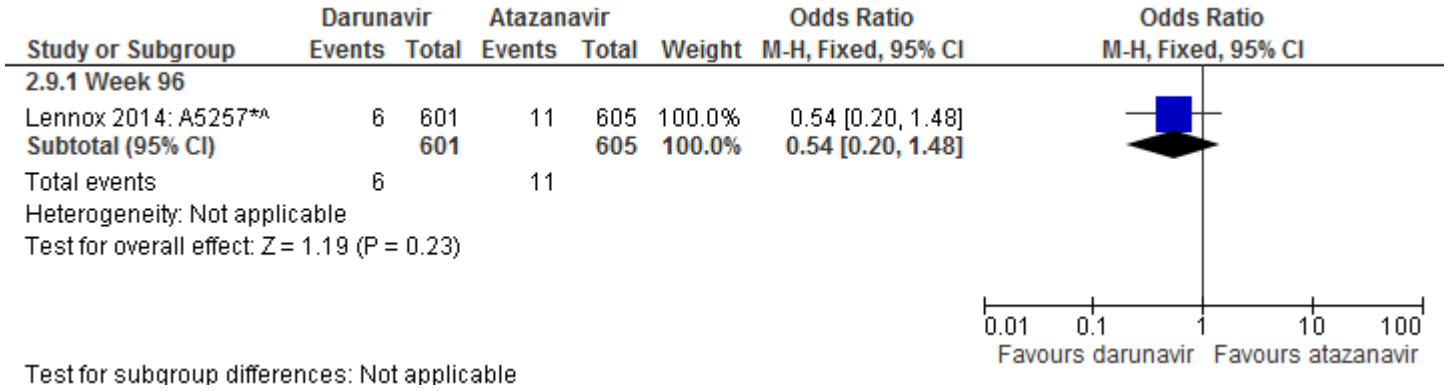


Forest plot of comparison: 2 Darunavir/ritonavir + tenofovir/emtricitabine versus atazanavir + tenofovir/emtricitabine, outcome: 2.7 Grade 3-4 adverse events (laboratory).



Forest plot of comparison: 2 Darunavir/ritonavir + tenofovir/emtricitabine versus atazanavir + tenofovir/emtricitabine, outcome: 2.8 Grade 3-4 headache.

Forest plot of comparison: 2 Darunavir/ritonavir + tenofovir/emtricitabine versus atazanavir + tenofovir/emtricitabine, outcome: 2.9 Grade 3-4 diarrhoea.



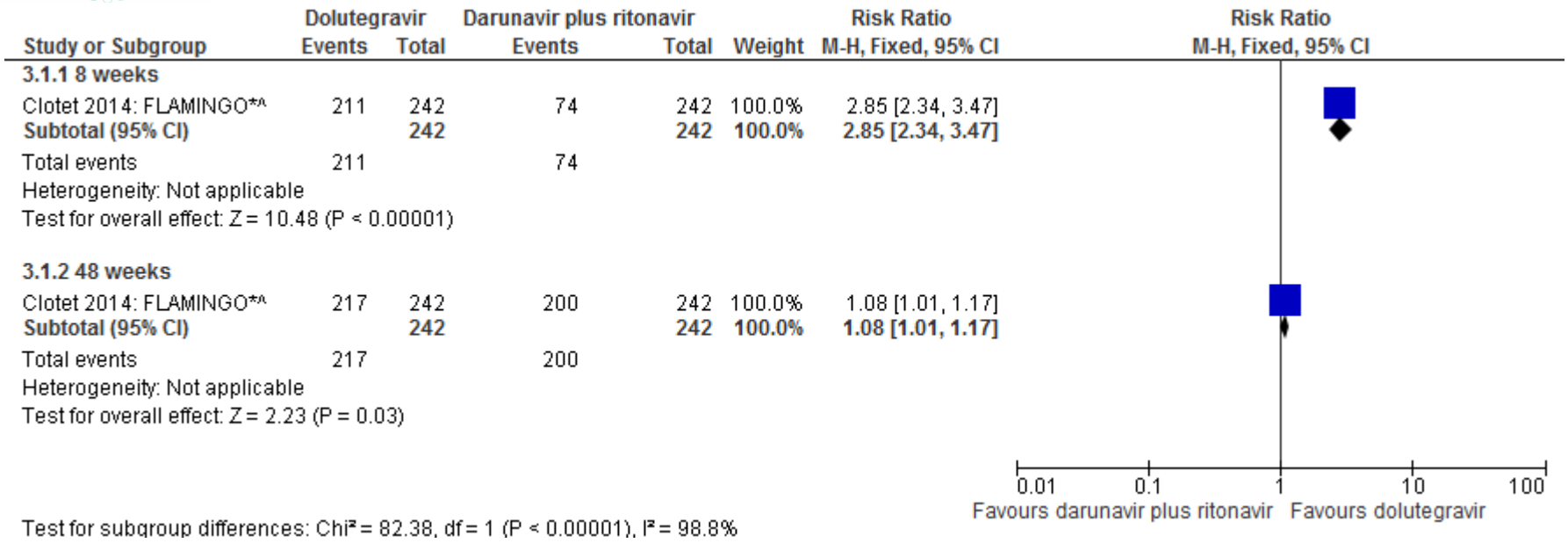
No data on Grade 3-4 rash, AST or ALT.

3 Dolutegravir versus darunavir plus ritonavir, with investigator-selected tenofovir–emtricitabine or abacavir–lamivudine

Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
Bonaventura Clotet, et al, on behalf of the ING114915 Study Team. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet 2014; 383: 2222–31	RCT: phase 3b, randomised, open-label, active-controlled, multicentre, parallel-group, non-inferiority study Randomisation: The study statistician generated the list using validated randomisation software; stratified by HIV-1 RNA and NRTI backbone. Allocation concealment: assigned (1:1) via a central interface Blinding: No masking was done in this study. Comparable groups at baseline: Baseline demographics and disease characteristics were similar between treatment groups Sample size calculation: With an assumed 80% response rate in the darunavir plus ritonavir group, the authors needed to enrol 234	488 randomised	Eligible patients (aged ≥18 years) had a concentration of plasma HIV-1 RNA of 1000 copies per mL or higher, no previous treatment with antiretroviral therapy, and no primary resistance to NRTIs or protease inhibitors. Excluded: Patients with active disease of category C from the Centers for Disease Control and Prevention, and defined laboratory values or medical characteristics such as pregnancy, moderate or severe hepatic impairment, an anticipated need for hepatitis C treatment during the study, estimated creatinine clearance of less than 50 mL/min (due to use of fixed-dose NRTI combinations), recent (within the	Dolutegravir 50 mg once daily. At the investigators' discretion, patients received an NRTI backbone of coformulated tenofovir–emtricitabine or abacavir–lamivudine.	Darunavir 800 mg plus ritonavir 100 mg once daily. At the investigators' discretion, patients received an NRTI backbone of coformulated tenofovir–emtricitabine or abacavir–lamivudine.	96 weeks (this paper reports up to 48 weeks)	The pre-specified primary endpoint was the proportion of patients with a concentration of HIV-1 RNA lower than 50 copies per mL at week 48, using the US Food and Drug Administration (FDA) snapshot (missing, switch, or discontinuation equals failure; MSDF) algorithm. Secondary endpoints included changes from baseline in CD4 cell counts, incidence and severity of adverse events, changes in laboratory variables (such as fasting low-density lipoprotein [LDL] cholesterol), time to virological suppression, and treatment-emergent genotypic or phenotypic evidence of resistance. Other secondary endpoints were disease progression, proportion of patients who discontinued treatment because of adverse events, and health outcomes measures, including the EuroQol five dimension (EQ-5D), HIV Treatment Satisfaction Questionnaire, and Symptom Distress Module. The non-inferiority margin was	ViiV Healthcare and Shionogi & Co.

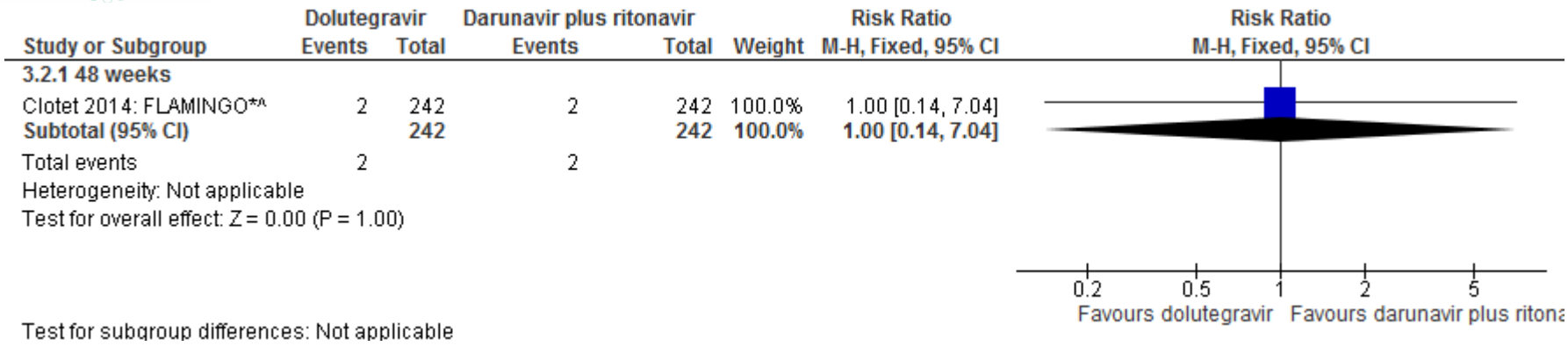
	evaluable patients per group to have 90% power with a 12% non-inferiority margin and a one-sided 2.5% significance level Intention to treat analysis: The authors did the analyses on the modified intention-to-treat exposed or modified safety populations, which consisted of all patients randomly assigned to treatment groups who received at least one dose of study drug, excluding one patient at one study site in Russia that was closed early after the sponsor became aware of issues of non-compliance to good clinical practice in another ViiV Healthcare-sponsored study. Drop out: 16/488 (3%) lost to follow up Setting: 64 research centres in France, Germany, Italy, Puerto Rico, Romania, Russia, Spain, Switzerland, and the USA		past 5 years) or ongoing malignancy, or treatment with an HIV-1 vaccine within 90 days of screening or with any immunomodulator within 28 days. Patients could receive abacavir–lamivudine only after screening negative for the HLA-B57*01 allele.				set as 12%	

Forest plot of comparison: 3 Dolutegravir versus darunavir plus ritonavir, with investigator-selected tenofovir–emtricitabine or abacavir–lamivudine, outcome: 3.1 Plasma HIV-1 RNA <50 copies per mL.



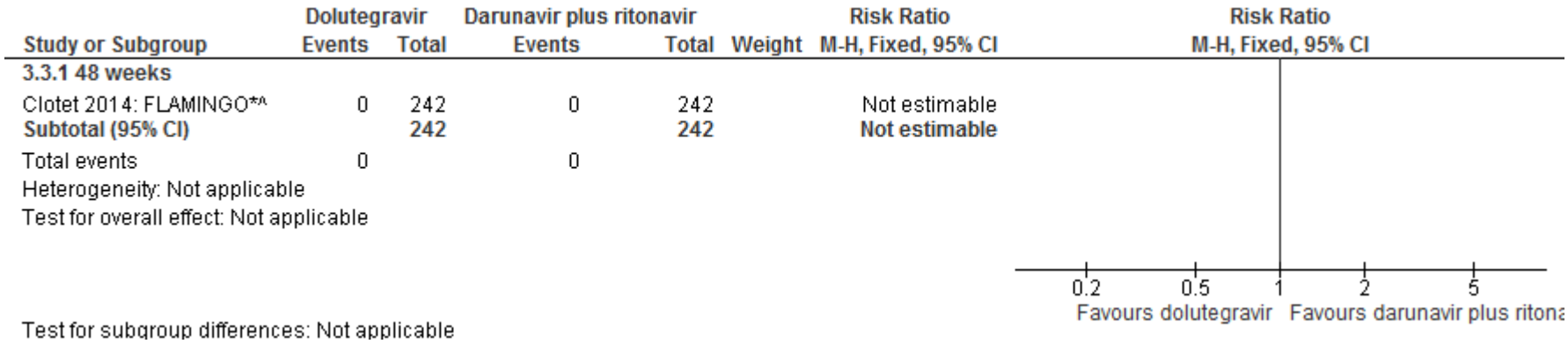
Subgroups by < or > 100,000 copies/mL at baseline not shown in Clotet 2014.

Forest plot of comparison: 3 Dolutegravir versus darunavir plus ritonavir, with investigator-selected tenofovir–emtricitabine or abacavir–lamivudine, outcome: 3.2 Virological failure.



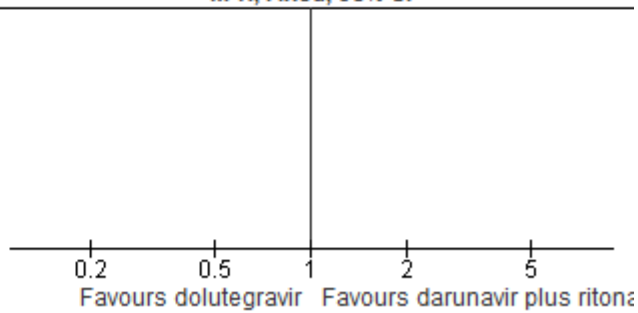
Subgroups by < or > 100,000 copies/mL at baseline not shown in Clotet 2014.

Forest plot of comparison: 3 Dolutegravir versus darunavir plus ritonavir, with investigator-selected tenofovir–emtricitabine or abacavir–lamivudine, outcome: 3.3 Resistance (% of total patients).



Forest plot of comparison: 3 Dolutegravir versus darunavir plus ritonavir, with investigator-selected tenofovir–emtricitabine or abacavir–lamivudine, outcome: 3.4 Resistance (% of those with virological failure).

Study or Subgroup	Dolutegravir Events	Total	Darunavir plus ritonavir Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 48 weeks						
Clotet 2014: FLAMINGO*^	0	2	0	2		Not estimable
Subtotal (95% CI)		**2**		**2**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Test for subgroup differences: Not applicable

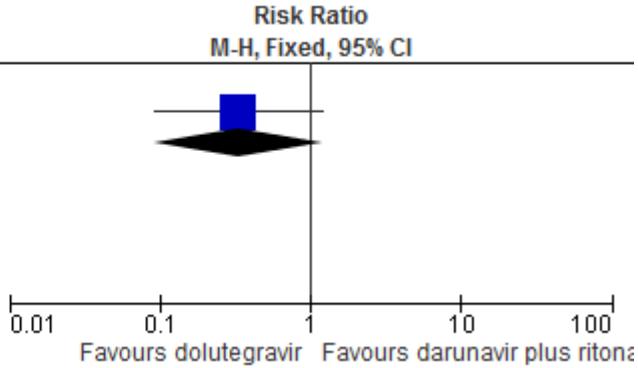
Four patients had protocol-defined virological failure; two in the dolutegravir group (HIV-1 RNA at protocol-defined virological failure 2270 and 668 copies per mL, week 24 for each) and two in the darunavir plus ritonavir group (HIV-1 RNA of 218 copies per mL at protocol-defined virological failure, week 48; and HIV-1 RNA of 61 754 copies per mL at protocol-defined virological failure, week 36). Both patients in the dolutegravir group received tenofovir–emtricitabine as the NRTI backbone, whereas the two patients in the darunavir plus ritonavir group received abacavir–lamivudine as the NRTI backbone. None of these patients had treatment-emergent primary integrase inhibitor, protease inhibitor, or NRTI resistance.

Forest plot of comparison: 3 Dolutegravir versus darunavir plus ritonavir, with investigator-selected tenofovir–emtricitabine or abacavir–lamivudine, outcome: 3.5 Discontinued due to adverse event or death.

Study or Subgroup	Dolutegravir Events	Total	Darunavir plus ritonavir Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.5.1 48 weeks						
Clotet 2014: FLAMINGO*^	3	242	9	242	100.0%	0.33 [0.09, 1.22]
Subtotal (95% CI)		**242**		**242**	**100.0%**	**0.33 [0.09, 1.22]**
Total events	3		9			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.66 (P = 0.10)



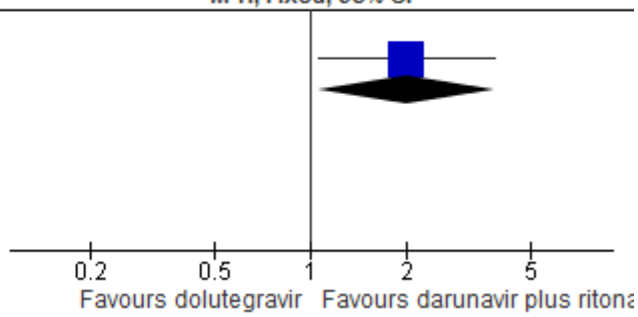
Test for subgroup differences: Not applicable

Forest plot of comparison: 3 Dolutegravir versus darunavir plus ritonavir, with investigator-selected tenofovir–emtricitabine or abacavir–lamivudine, outcome: 3.6 Any serious adverse event (clinical).

Study or Subgroup	Dolutegravir Events	Total	Darunavir plus ritonavir Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.6.1 48 weeks						
Clotet 2014: FLAMINGO*^	26	242	13	242	100.0%	2.00 [1.05, 3.80]
Subtotal (95% CI)		**242**		**242**	**100.0%**	**2.00 [1.05, 3.80]**
Total events	26		13			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.12 (P = 0.03)



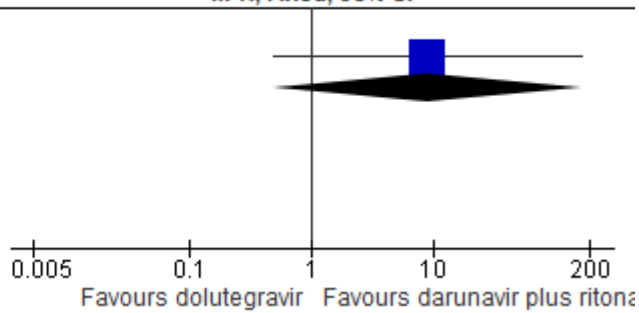
Test for subgroup differences: Not applicable

Forest plot of comparison: 3 Dolutegravir versus darunavir plus ritonavir, with investigator-selected tenofovir–emtricitabine or abacavir–lamivudine, outcome: 3.7 Serious adverse event: nervous system disorders.

Study or Subgroup	Dolutegravir Events	Dolutegravir Total	Darunavir plus ritonavir Events	Darunavir plus ritonavir Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.7.1 48 weeks						
Clotet 2014: FLAMINGO*^	4	242	0	242	100.0%	9.00 [0.49, 166.26]
Subtotal (95% CI)		**242**		**242**	**100.0%**	**9.00 [0.49, 166.26]**
Total events	4		0			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.48 (P = 0.14)



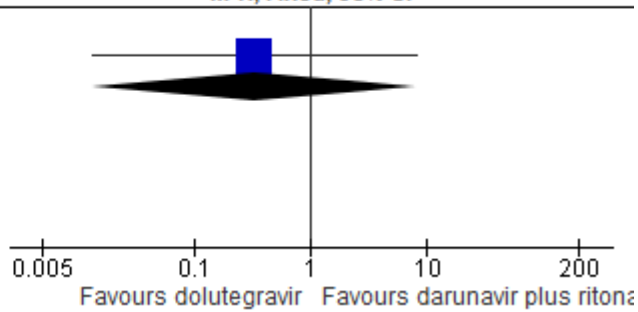
Test for subgroup differences: Not applicable

Forest plot of comparison: 3 Dolutegravir versus darunavir plus ritonavir, with investigator-selected tenofovir–emtricitabine or abacavir–lamivudine, outcome: 3.8 Serious adverse event: diarrhoea.

Study or Subgroup	Dolutegravir Events	Dolutegravir Total	Darunavir plus ritonavir Events	Darunavir plus ritonavir Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.8.1 48 weeks						
Clotet 2014: FLAMINGO*^	0	242	1	242	100.0%	0.33 [0.01, 8.14]
Subtotal (95% CI)		**242**		**242**	**100.0%**	**0.33 [0.01, 8.14]**
Total events	0		1			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.67 (P = 0.50)



Test for subgroup differences: Not applicable

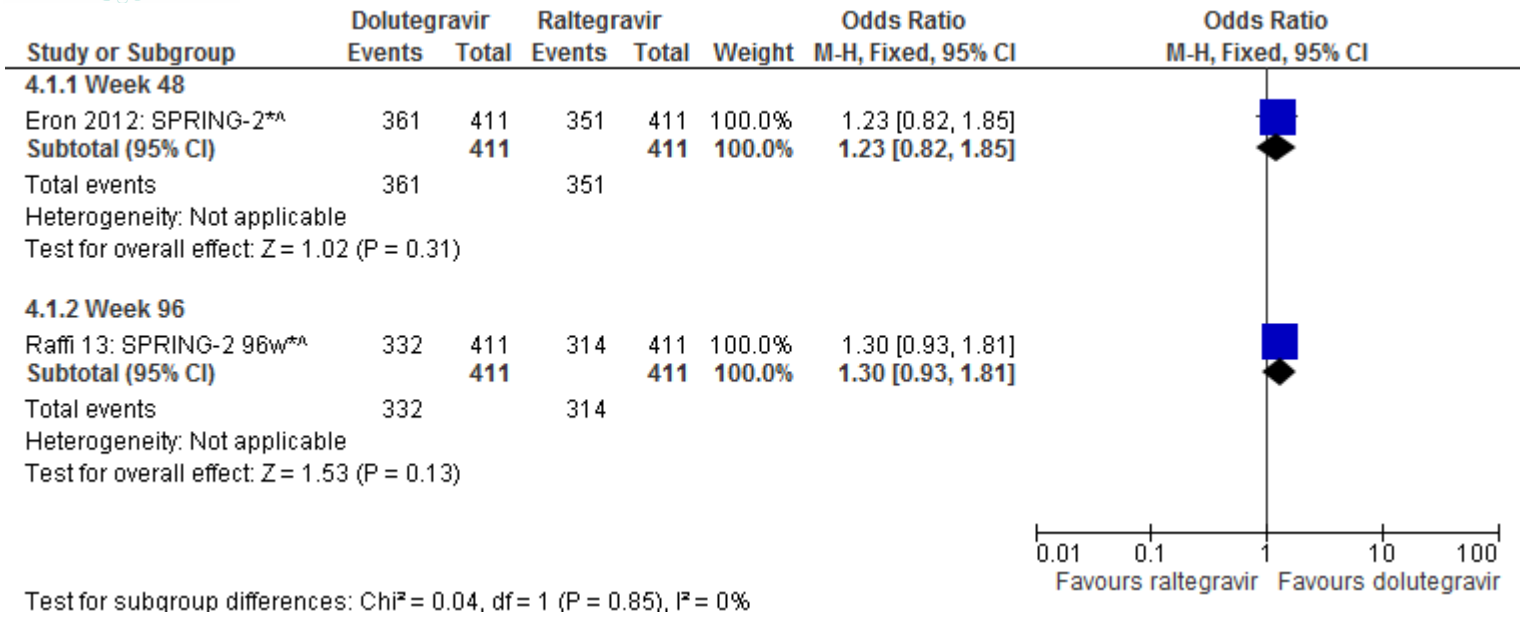
No data for Grade 3-4 adverse events (laboratory), rash or AST/ALT.

4 Dolutegravir versus raltegravir, with investigator-selected NRTIs (TDF/FTC or ABC/3TC)

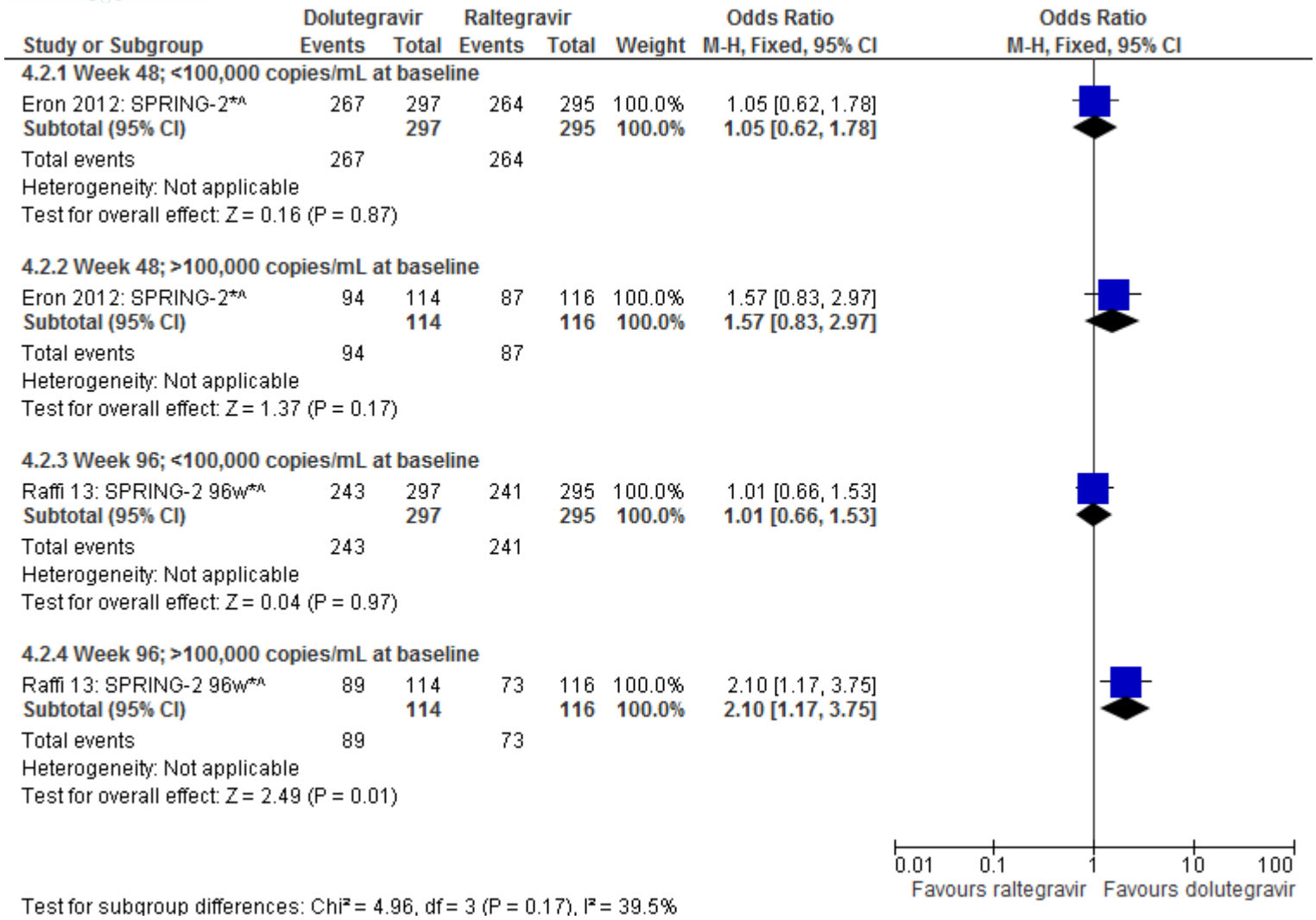
Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
Eron Jr, J et al for the SPRING-2 & SINGLE Study Teams. Dolutegravir treatment response by baseline viral load and NRTI backbone in treatment-naıve HIV-infected individuals. Journal of the International AIDS Society 2012, 15 (Suppl 4): 18264 Francois Raffi et al on behalf of the SPRING-2 study group. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet 2013; 381: 735–43 François Raffi et al	Design: phase 3, randomised, double-blind, active-controlled, non-inferiority study (NCT01227824) SPRING-2 Randomisation: randomly assigned (1:1) via a central procedure using phone and web interface; study statistician generated the randomisation list with GlaxoSmithKline-validated randomisation software (RandAll); stratified by screening HIV-1 RNA (≤100 000 copies per mL or >100 000 copied per mL) and NRTI backbone. Allocation concealment: central procedure using phone and web interface Blinding: Investigators were unmasked to screening HIV-1 RNA results before randomisation. Sponsor staff were masked to treatment assignment until the week 48 analysis; investigators, site staff and patients were masked until week 96. Comparable groups at baseline: Baseline demographics and disease characteristics were similar between treatment groups Sample size calculation: The authors concluded non-inferiority of dolutegravir to raltegravir if the lower bound of a two-sided 95% CI for the difference in proportions (dolutegravir minus raltegravir) of patients with plasma HIV-1 RNA less than 50 copies	827 randomised; 822 received at least one dose of study drug (4 withdrew consent; 1 not treatment-naïve)	Inclusion: Eligible participants (aged ≥18 years) had a plasma HIV-1 RNA concentration of 1000 copies per mL or greater and no primary resistance in reverse transcriptase or protease enzymes; no CD4 entry criteria. Excluded: patients with active US Centers for Disease Control and Prevention category C disease, except for Kaposi's sarcoma; patients with defined laboratory values or medical characteristics, including pregnancy; moderate or severe hepatic impairment; an anticipated need for hepatitis C treatment during the study; estimated creatinine clearance of less than 50 mL/min; recent or ongoing malignancy; or treatment with an HIV-1 vaccine within 90 days of screening or with any immunomodulator within 28 days. Patients could receive abacavir only	Dolutegravir 50 mg once daily, in combination with investigator-selected NRTIs (TDF/FTC or ABC/3TC) n=411, of whom: 132 had baseline <100,000 copies/mL and received ABC/3TC; 165 had baseline <100,000 copies/mL and received TDF/FTC; 37 had baseline >100,000 copies/mL and received ABC/3TC; and 77 had baseline >100,000 copies/mL and received TDF/FTC	Raltegravir 400 mg twice daily, in combination with investigator-selected NRTIs (TDF/FTC or ABC/3TC) n=411, of whom: 125 had baseline <100,000 copies/mL and received ABC/3TC; 170 had baseline <100,000 copies/mL and received TDF/FTC; 39 had baseline >100,000 copies/mL and received ABC/3TC;	96 weeks	The pre-specified primary endpoint was the proportion of patients with HIV-1 RNA of less than 50 copies per mL at week 48. Main secondary endpoints were changes from baseline in CD4 cell counts, incidence and severity of adverse events, changes in laboratory parameters, and genotypic or phenotypic evidence of resistance. Other secondary endpoints were dolutegravir pharmacokinetics, pharmacokinetic and pharmacodynamic relations, and health	ViiV Healthcare.

on behalf of the extended SPRING-2 Study Group. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis 2013; 13: 927–35	per mL at week 48 was greater than –10%. With an assumed 75% response rate in the raltegravir group, the authors needed to enrol 394 evaluable patients per group to have 90% power with a 10% non-inferiority margin, and a one-sided 2·5% significance level. The study was not fully powered for secondary or subgroup analyses. Intention to treat analysis: The authors based their efficacy and safety analyses on the intent-to-treat exposed or safety populations, which consisted of all patients randomly assigned to treatment groups who received at least one dose of study drug. Drop out: 24 protocol deviation; 11 lost to follow up; 11 withdrew consent (total 46/822 [5.6%]) Setting: 100 sites in the USA, Canada, Europe, and Australia		after exclusion of the HLA-B*5701 allele.		and 77 had baseline >100,000 copies/mL and received TDF/FTC		outcomes. The authors used EQ-5D (EuroQol, Rotterdam, Netherlands), a generic, non-disease-specific, preference-based utility measure that includes a descriptive system and a visual analogue scale, to measure health outcome at baseline and weeks 24, 48, and 96.	

Forest plot of comparison: 4 Dolutegravir versus raltegravir, with investigator-selected NRTIs (TDF/FTC or ABC/3TC), outcome: 4.1 HIV-1 RNA <50/mL.

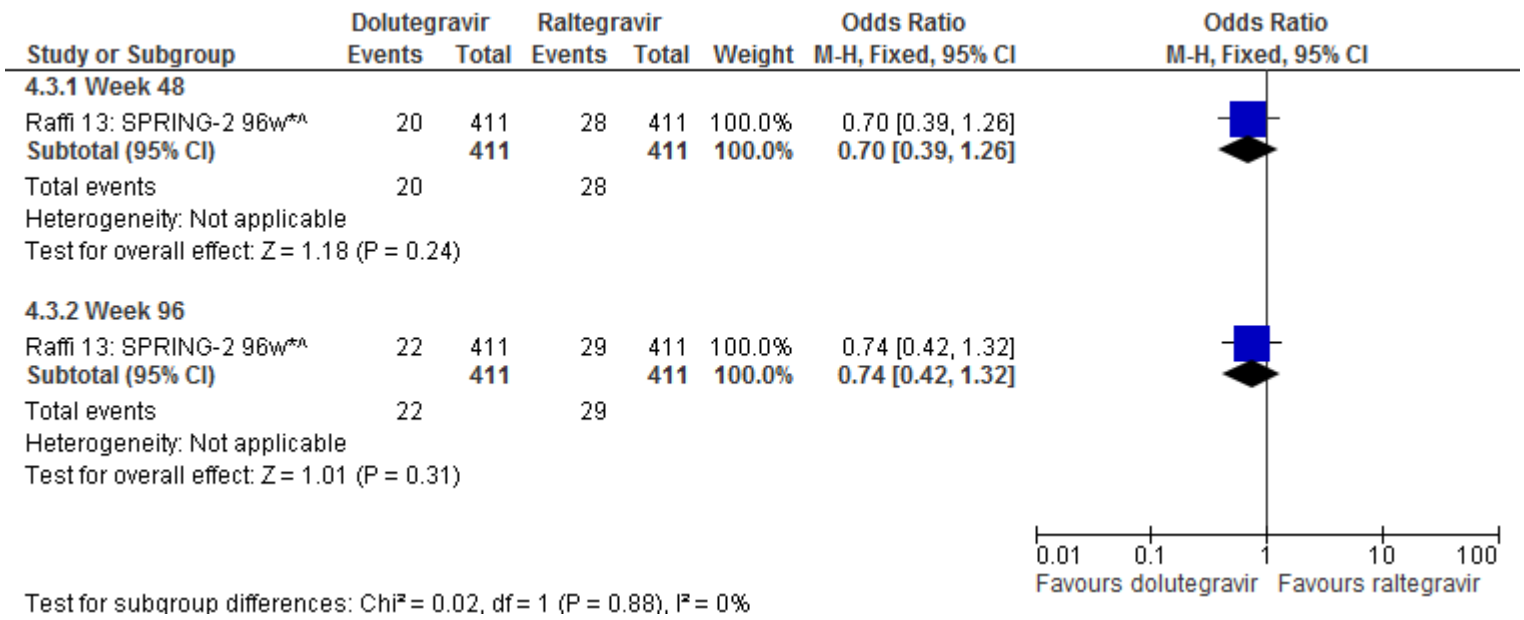


Forest plot of comparison: 4 Dolutegravir versus raltegravir, with investigator-selected NRTIs (TDF/FTC or ABC/3TC), outcome: 4.2 HIV-1 RNA <50/mL; subgroups.



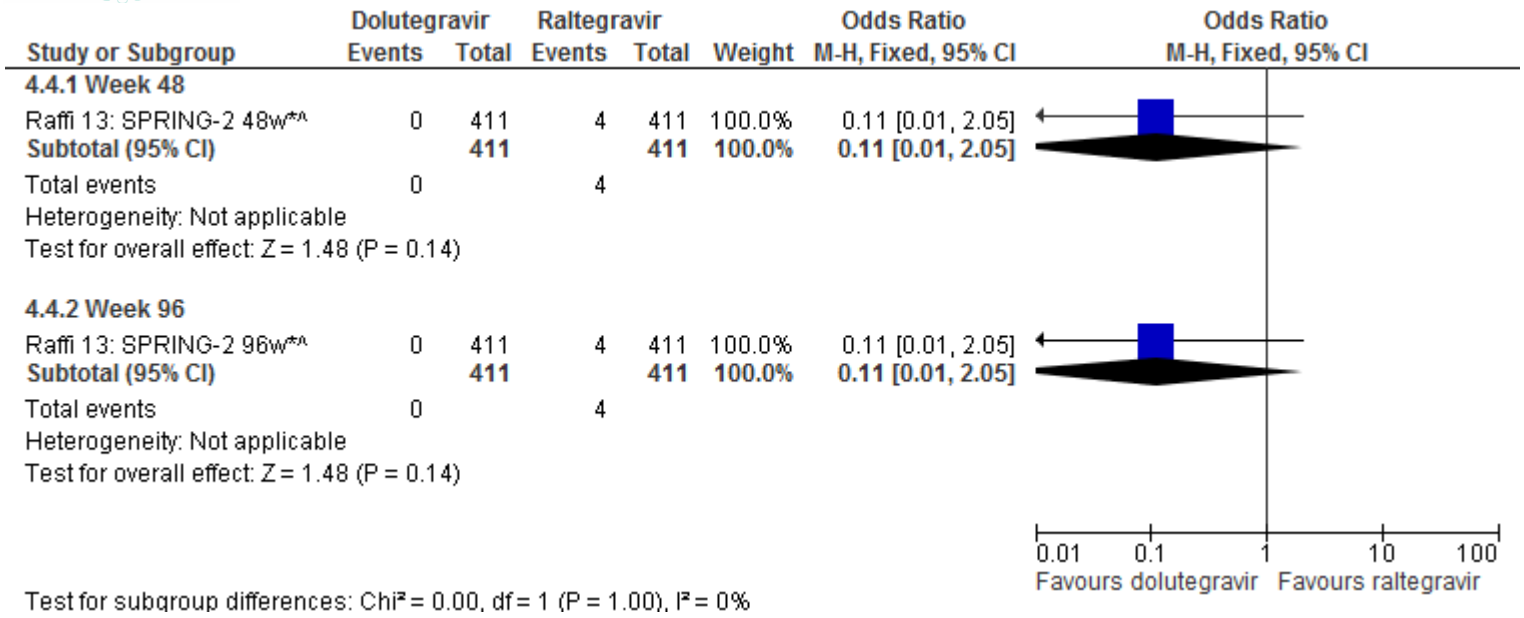
Test for subgroup differences: Chi² = 4.96, df = 3 (P = 0.17), I² = 39.5%

Forest plot of comparison: 4 Dolutegravir versus raltegravir, with investigator-selected NRTIs (TDF/FTC or ABC/3TC), outcome: 4.3 Virological failure.

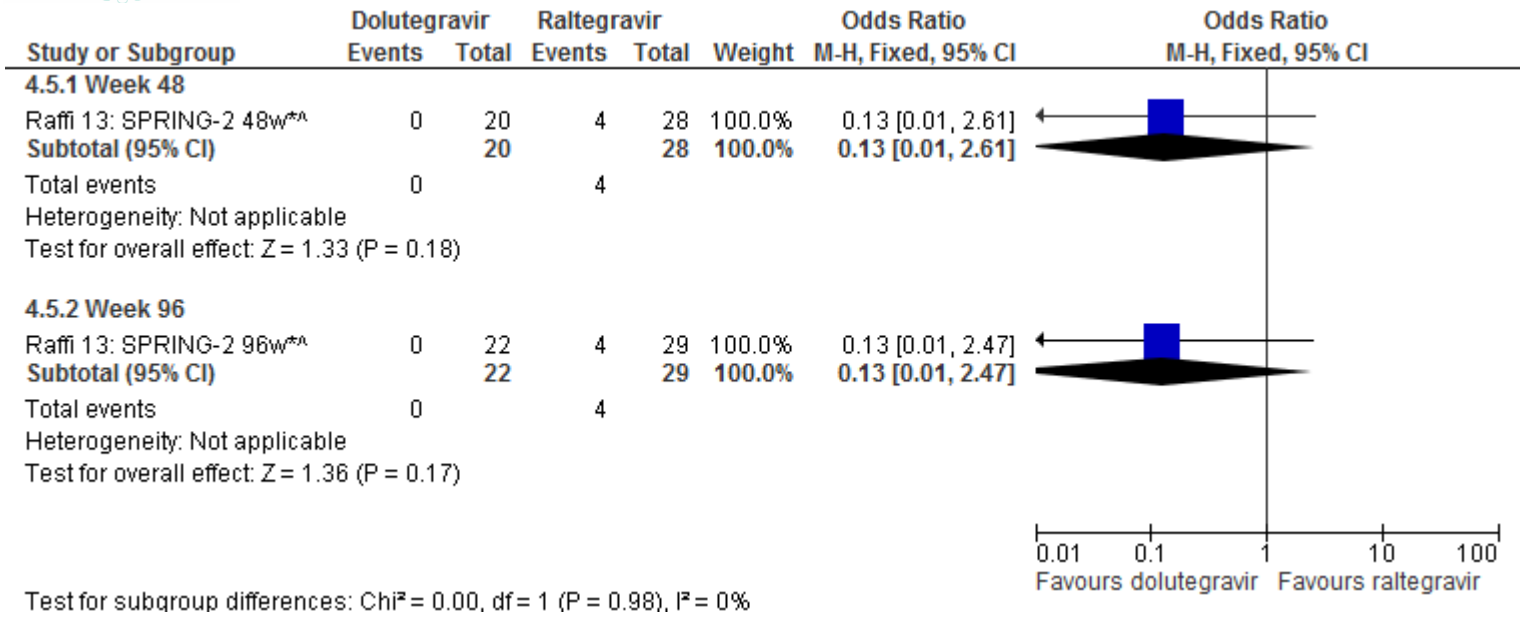


Subgroups not available for protocol-defined virological failure in Raffi 2013.

Forest plot of comparison: 4 Dolutegravir versus raltegravir, with investigator-selected NRTIs (TDF/FTC or ABC/3TC), outcome: 4.4 Resistance (% total population).

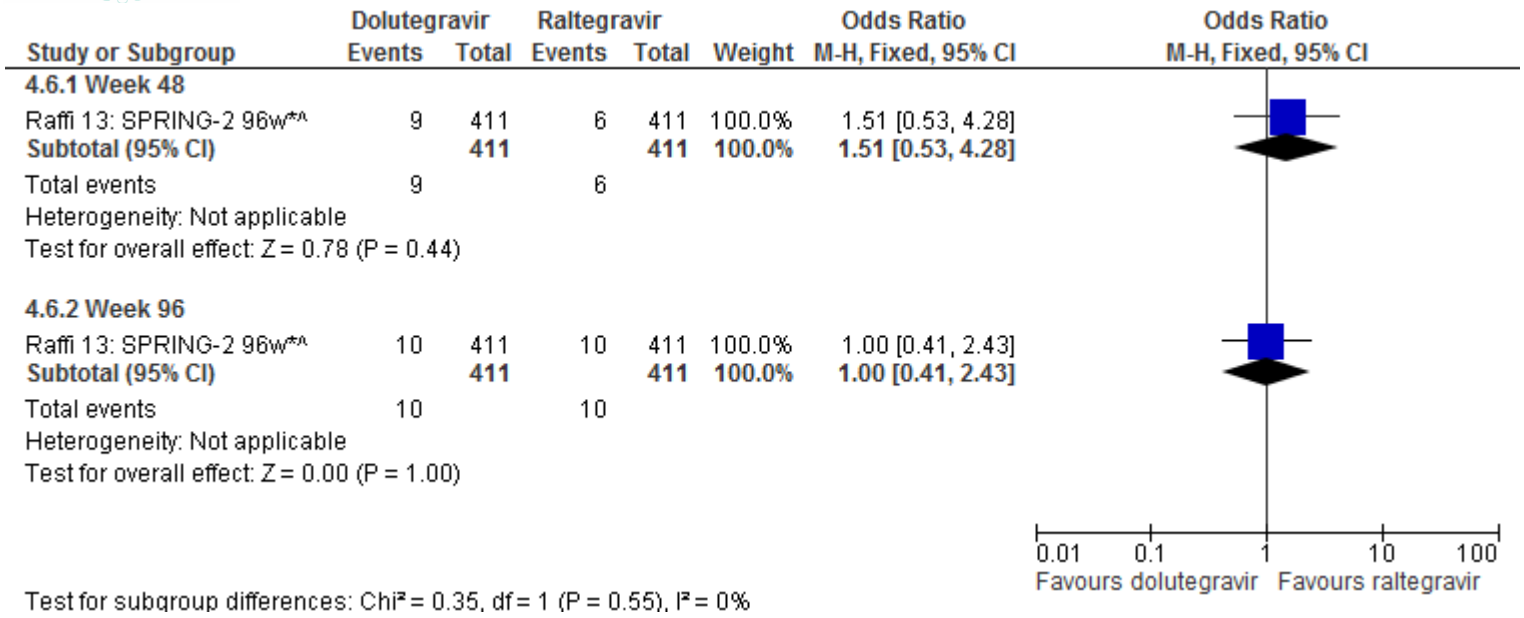


Forest plot of comparison: 4 Dolutegravir versus raltegravir, with investigator-selected NRTIs (TDF/FTC or ABC/3TC), outcome: 4.5 Resistance (% those with virological failure).

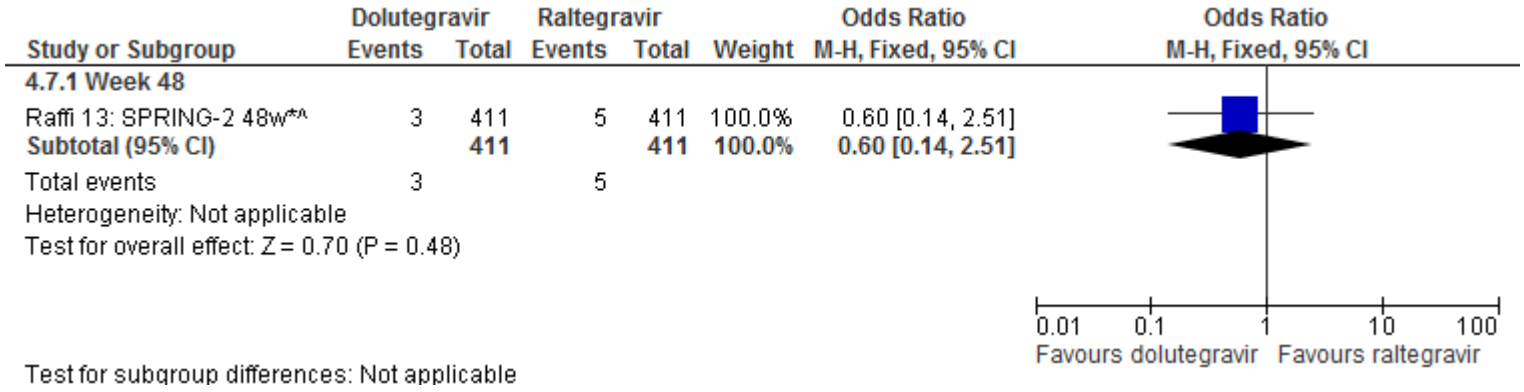


At 48 weeks, no patient with protocol-defined virological failure who received dolutegravir had treatment-emergent integrase or NRTI resistance. Notably, one patient in the raltegravir group with baseline plasma HIV-1 RNA of more than 3 million copies per mL developed both integrase-resistant and NRTI-resistant mutations; phenotype resistance at virological failure showed a raltegravir fold-change of 34 and a dolutegravir fold-change of 2.02. At 96 weeks, no further patients had resistance.

Forest plot of comparison: 4 Dolutegravir versus raltegravir, with investigator-selected NRTIs (TDF/FTC or ABC/3TC), outcome: 4.6 Discontinued due to adverse event or death.



Forest plot of comparison: 4 Dolutegravir versus raltegravir, with investigator-selected NRTIs (TDF/FTC or ABC/3TC), outcome: 4.7 Drug-related serious adverse events.

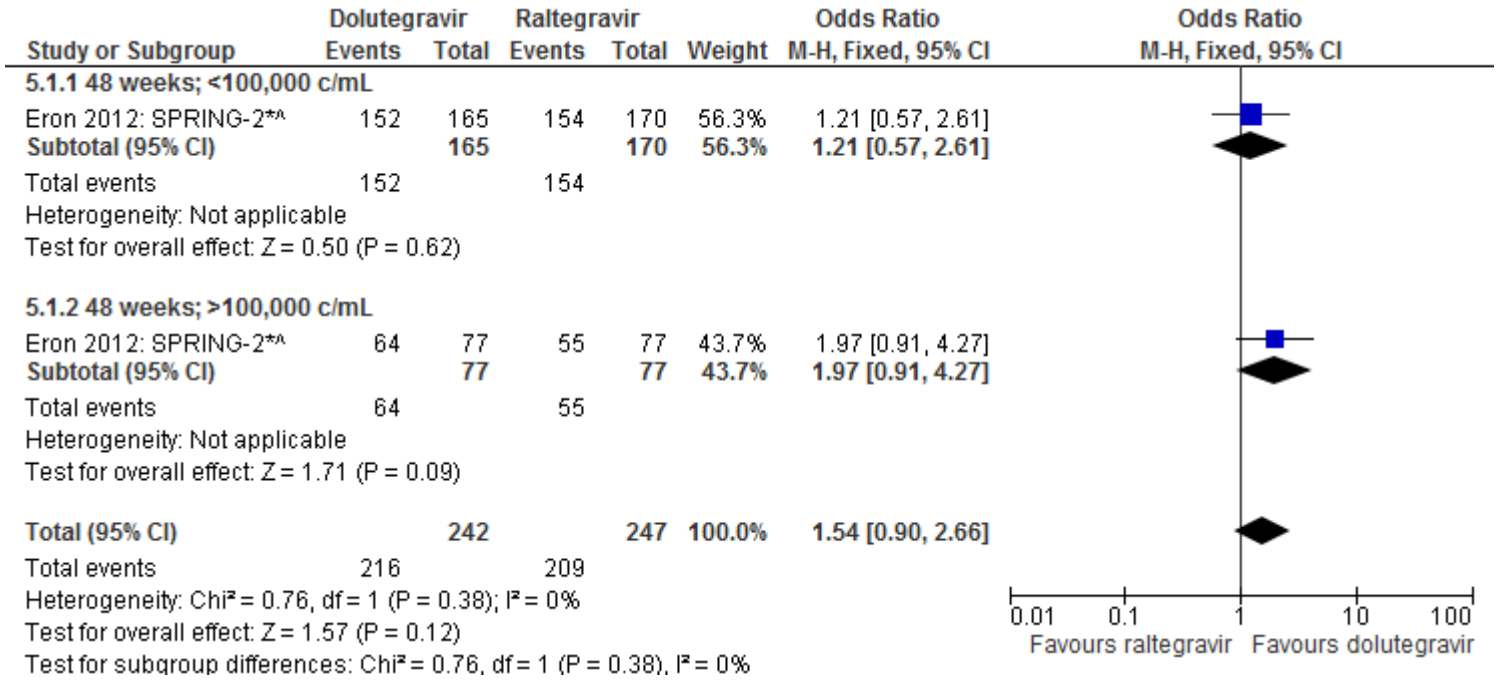


No data on Grade 3-4 adverse events (laboratory), rash, AST/ALT, CNS events or diarrhoea.

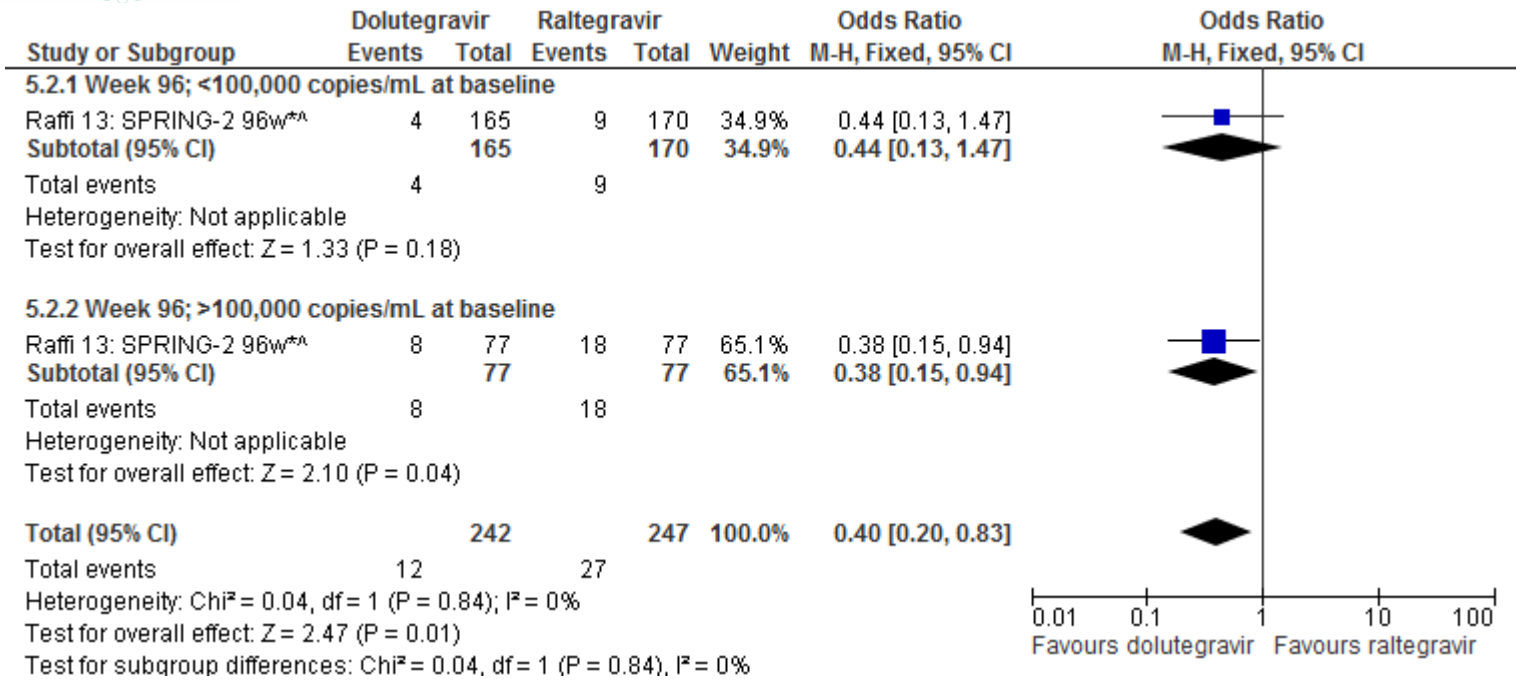
5 Dolutegravir/TDF/FTC versus raltegravir/TDF/FTC; subgroups by baseline viral load

This section is a sub-group of the above study SPRING-2 in section 4, where the patients received TDF/FTC with the randomised comparison of dolutegravir versus raltegravir (see above for evidence table).

Forest plot of comparison: 5 Dolutegravir/TDF/FTC versus raltegravir/TDF/FTC; subgroups by baseline viral load, outcome: 5.1 HIV-1 RNA <50/mL.



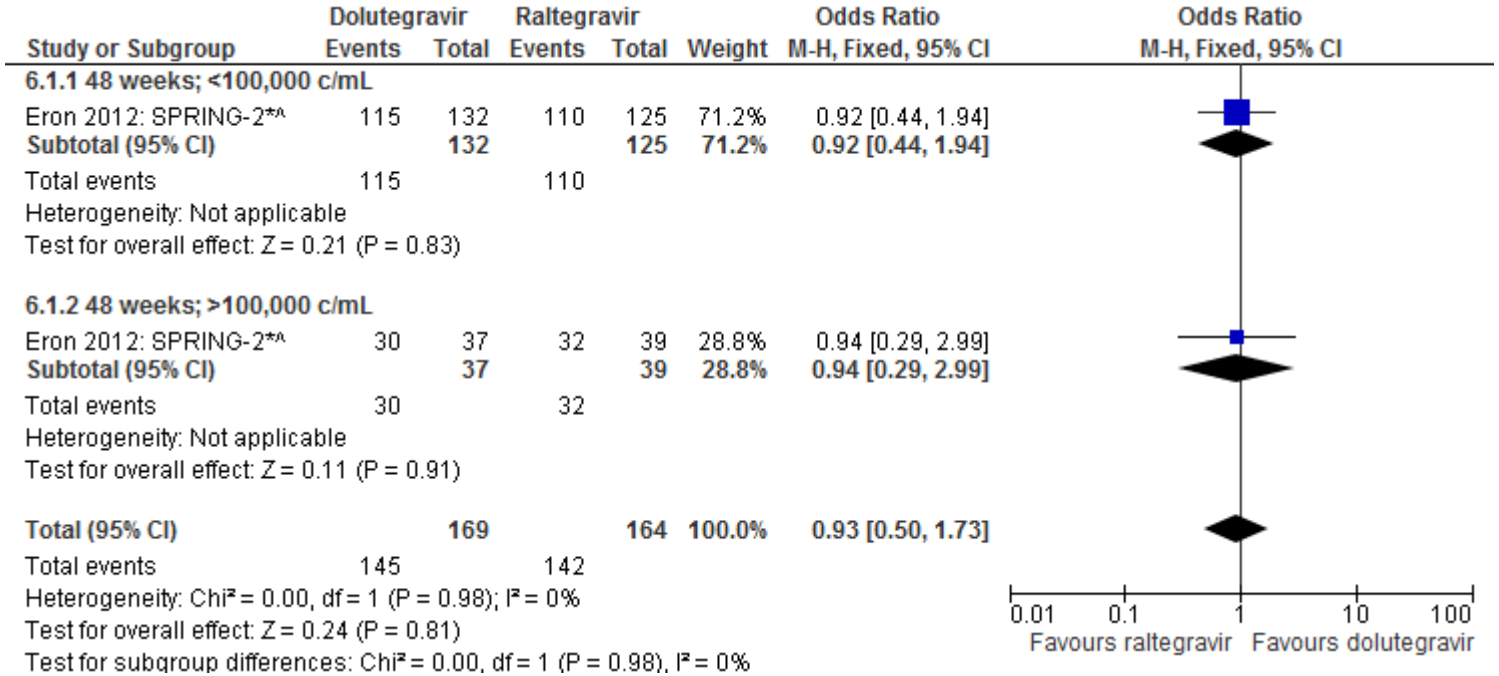
Forest plot of comparison: 5 Dolutegravir/TDF/FTC versus raltegravir/TDF/FTC; subgroups by baseline viral load, outcome: 5.2 Virological failure.


Dolutegravir
Raltegravir
Odds Ratio
Odds Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
5.2.1 Week 96; <100,000 copies/mL at baseline
Raffi 13: SPRING-2 96w*^ 4 165 9 170 34.9% 0.44 [0.13, 1.47]
Subtotal (95% CI) 165 170 34.9% 0.44 [0.13, 1.47]
Total events 4 9
Heterogeneity: Not applicable
Test for overall effect: Z = 1.33 (P = 0.18)
5.2.2 Week 96; >100,000 copies/mL at baseline
Raffi 13: SPRING-2 96w*^ 8 77 18 77 65.1% 0.38 [0.15, 0.94]
Subtotal (95% CI) 77 77 65.1% 0.38 [0.15, 0.94]
Total events 8 18
Heterogeneity: Not applicable
Test for overall effect: Z = 2.10 (P = 0.04)
Total (95% CI) 242 247 100.0% 0.40 [0.20, 0.83]
Total events 12 27
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 2.47 (P = 0.01)
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%
0.01
0.1
1
10
100
Favours dolutegravir
Favours raltegravir

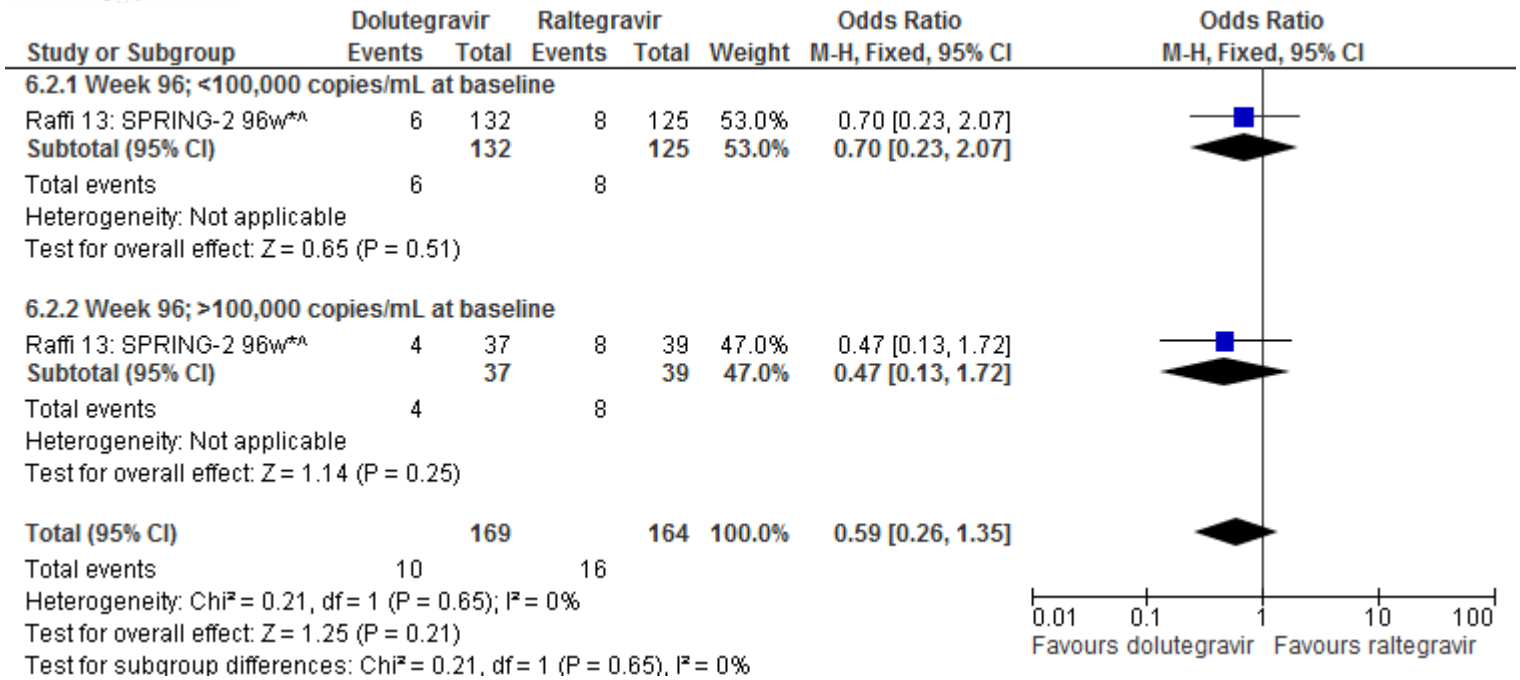
6 Dolutegravir/ABC/3TC versus raltegravir/ABC/3TC; subgroups by baseline viral load

This section is a sub-group of the above study SPRING-2 in section 4, where the patients received ABC/3TC with the randomised comparison of dolutegravir versus raltegravir (see above for evidence table).

Forest plot of comparison: 6 Dolutegravir/ABC/3TC versus raltegravir/ABC/3TC; subgroups by baseline viral load, outcome: 6.1 HIV-1 RNA <50/mL.



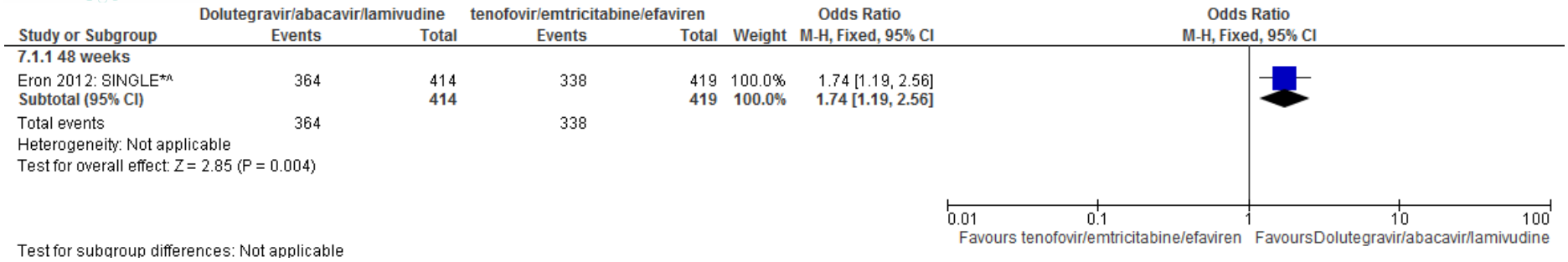
Forest plot of comparison: 6 Dolutegravir/ABC/3TC versus raltegravir/ABC/3TC; subgroups by baseline viral load, outcome: 6.2 Virological failure.


Dolutegravir
Raltegravir
Odds Ratio
Odds Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
6.2.1 Week 96; <100,000 copies/mL at baseline
Raffi 13: SPRING-2 96w*^ 6 132 8 125 53.0% 0.70 [0.23, 2.07]
Subtotal (95% CI) 132 125 53.0% 0.70 [0.23, 2.07]
Total events 6 8
Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.51)
6.2.2 Week 96; >100,000 copies/mL at baseline
Raffi 13: SPRING-2 96w*^ 4 37 8 39 47.0% 0.47 [0.13, 1.72]
Subtotal (95% CI) 37 39 47.0% 0.47 [0.13, 1.72]
Total events 4 8
Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.25)
Total (95% CI) 169 164 100.0% 0.59 [0.26, 1.35]
Total events 10 16
Heterogeneity: Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.25 (P = 0.21)
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%
0.01
0.1
1
10
100
Favours dolutegravir
Favours raltegravir

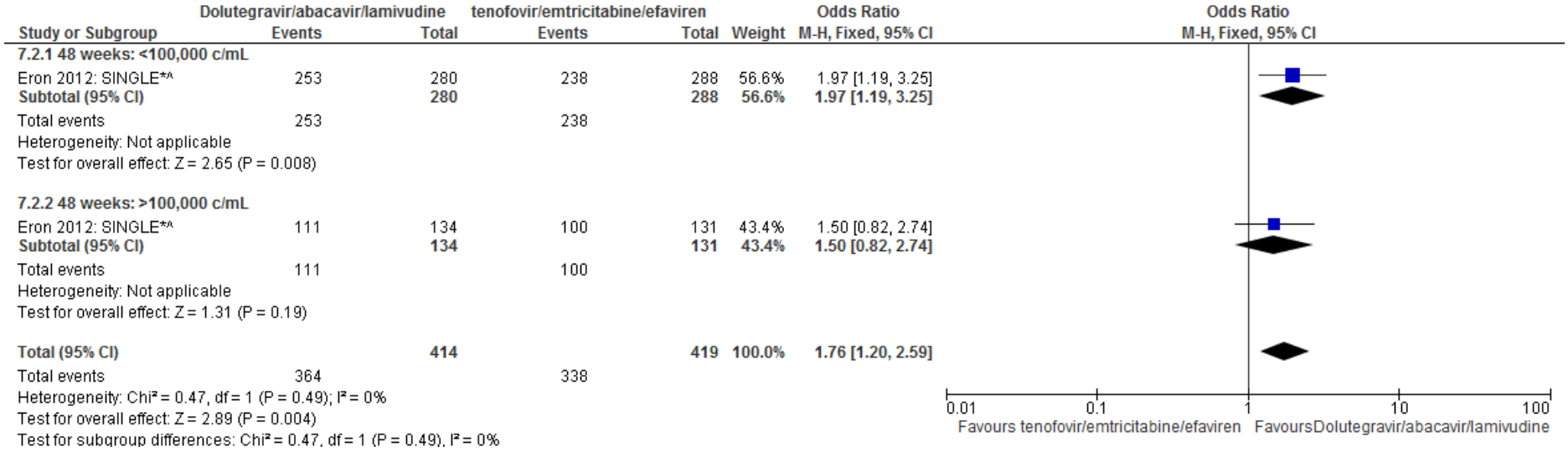
7 Dolutegravir/abacavir/lamivudine versus efavirenz/tenofovir/emtricitabine

Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
Eron Jr, J et al for the SPRING-2 & SINGLE Study Teams. Dolutegravir treatment response by baseline viral load and NRTI backbone in treatment-naıve HIV-infected individuals. Journal of the International AIDS Society 2012, 15 (Suppl 4): 18264 S. Walmsley et al. Dolutegravir (DTG; S/GSK1349572) + Abacavir/Lamivudine Once Daily Statistically Superior to Tenofovir/Emtricitabine/Efavirenz: 48-Week Results - SINGLE (ING114467). http://www.abstractsonline.com/Plan/ViewAbstract.aspx?mID=2963&sKey=e1c18d5b-830f-4b4e-8671-35bcfb20eed5&cKey=af219b7d-2171-46b2-91ef-b8049552c9e5&mKey=%7b6B114A1D-85A4-4054-A83B-04D8B9B8749F%7d ICAAC 2012 Conference Abstract	Design: double-blind, double-dummy, non-inferiority phase III study Randomisation: Not stated Allocation concealment: Not stated Blinding: Not stated Comparable groups at baseline: groups similar at baseline Sample size calculation: Not stated Intention to treat analysis: Not stated Drop out: Not stated Setting: Not stated	833 enrolled	Inclusion: therapy-naïve adults with HIV-1 RNA ≥1000 c/mL Exclusion: not stated	Dolutegravir 50 mg + ABC/3TC daily (n=414)	TDF/FTC/ EFV daily (n=419)	48 weeks	Proportion of subjects with HIV-1 RNA <50 c/mL at week 48 (FDA Snapshot, ITT-Exposed). Tolerability, safety, & viral resistance evaluated.	Probably GlaxoSmith-Kline

Forest plot of comparison: 7 Dolutegravir/abacavir/lamivudine versus efavirenz/tenofovir/emtricitabine, outcome: 7.1 HIV-1 RNA <50/mL.

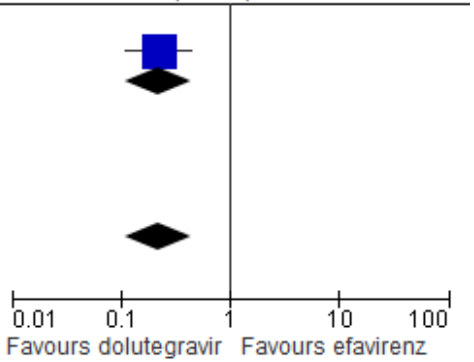


Forest plot of comparison: 7 Dolutegravir/abacavir/lamivudine versus efavirenz/tenofovir/emtricitabine, outcome: 7.2 HIV-1 RNA <50/mL: subgroups by baseline viral load.



Forest plot of comparison: 7 Dolutegravir/abacavir/lamivudine versus efavirenz/tenofovir/emtricitabine, outcome: 7.3 Discontinued due to adverse event.

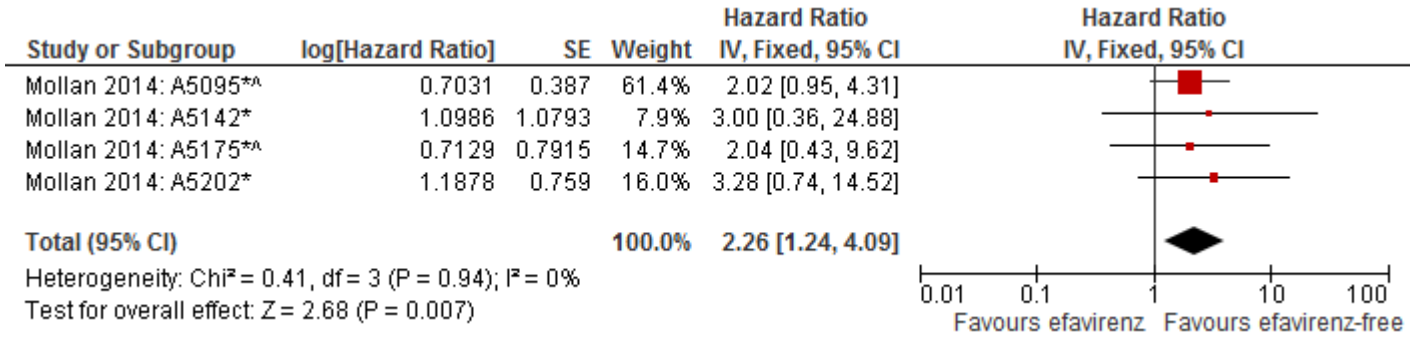
Study or Subgroup	Dolutegravir/abacavir/lamivudine Events	Total	tenofovir/emtricitabine/efaviren Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
7.3.1 Week 48						
Walmsley 12: SINGLE*^	10	414	42	419	100.0%	0.22 [0.11, 0.45]
Subtotal (95% CI)		**414**		**419**	**100.0%**	**0.22 [0.11, 0.45]**
Total events	10		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.19 (P < 0.0001)						
Total (95% CI)		**414**		**419**	**100.0%**	**0.22 [0.11, 0.45]**
Total events	10		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.19 (P < 0.0001)						
Test for subgroup differences: Not applicable						



8 Efavirenz versus efavirenz-free regimens

Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
Katie R. Mollan et al. Association Between Efavirenz as Initial Therapy for HIV-1 Infection and Increased Risk for Suicidal Ideation or Attempted or Completed Suicide An Analysis of Trial Data. Ann Intern Med 2014; 161:1-10. doi:10.7326/M14-0293	Design: Participant-level data were analyzed from 4 AIDS Clinical Trials Group antiretroviral-naive studies conducted from 2001 to 2010 (ClinicalTrials.gov: NCT00013520 [A5095], NCT00050895 [A5142], NCT00084136 [A5175], and NCT 00118898 [A5202]). Randomisation: Within each study, participants were randomly assigned to an efavirenz-containing (n = 3241) or efavirenz-free (n = 2091) regimen. Each study used permuted-block randomisation. Allocation concealment: Not stated Blinding: Efavirenz assignment was open-label in A5142, A5175 and A5202 and was blinded and placebo-controlled in A5095 before a data safety monitoring board (DSMB) recommendation to unblind efavirenz. Comparable groups at baseline: Baseline characteristics were balanced between groups through randomisation Sample size calculation: Not stated Intention to treat analysis: The primary analysis approach was intention-to-treat (ITT). Drop out: Not stated Setting: AIDS Clinical Trials Group sites; 74% of participants enrolled in the United States.	5332 randomised	Included: Antiretroviral-naive participants. Excluded: Each study excluded participants with substantially abnormal baseline laboratory values. Histories of suicidal ideation or attempt were not exclusion criteria.	Efavirenz-containing regimen (600mg once daily)	Efavirenz-free regimen	At least 96 weeks	Suicidality was defined as suicidal ideation or attempted or completed suicide. Groups were compared with a hazard ratio and 95% CI estimated from a Cox model, stratified by study.	The National Institute of Allergy and Infectious Diseases funded all 4 studies and this combined data analysis.

Forest plot of comparison: 8 Efavirenz versus efavirenz-free regimens, outcome: 8.1 Suicidality (suicidal ideation or attempted or completed suicide).



Not available by < or > 100,000 copies/mL at baseline.

9 Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild) versus efavirenz/ emtricitabine/ tenofovir disoproxil fumarate

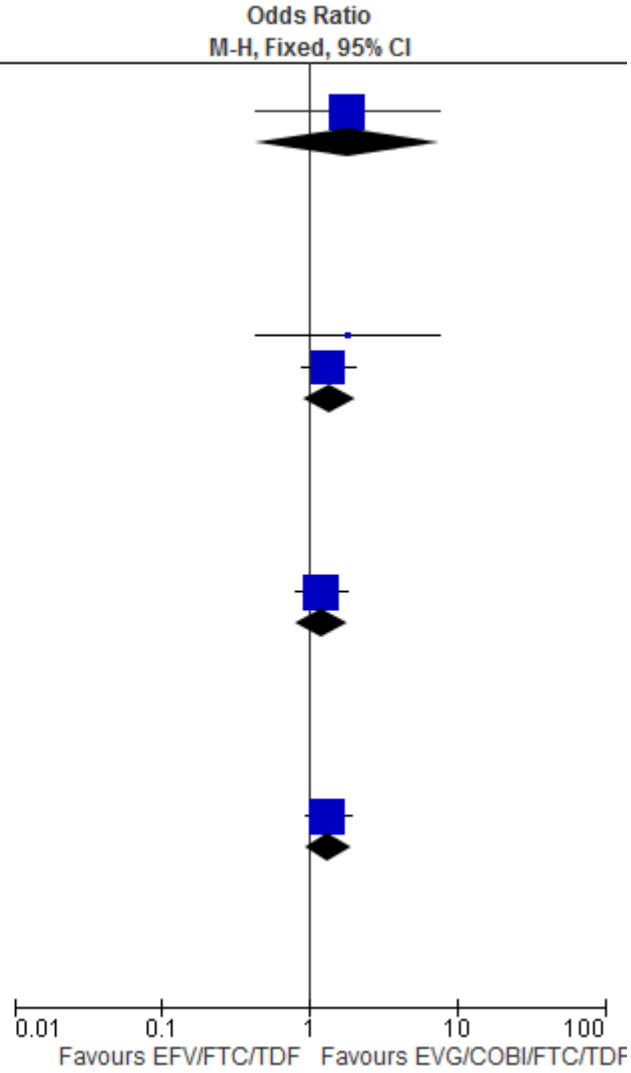
Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
Calvin Cohen et al. Randomized, phase 2 evaluation of two single-tablet regimens elvitegravir/ cobicistat/ emtricitabine/tenofovir disoproxil fumarate versus efavirenz/ emtricitabine/tenofovir disoproxil fumarate for the initial treatment of HIV infection. AIDS 2011, 25: F7–F12.	Design: Phase 2, randomized, double-blind, double-dummy, multicenter, active-controlled study (NCT00869557; study 104) Randomisation: computer generated; stratified by screening HIV-1 RNA level (≤ or > 100 000 copies/ml) in a 2 : 1 manner (block size of 6) Allocation concealment: randomised centrally by a third party interactive voice/web response system Blinding: participants received placebo tablets matching the alternate treatment. All parties involved in the study (patients, care providers and site, CRO and Sponsor staff) were blinded to treatment. Comparable groups at baseline: Baseline demographics and disease characteristics were similar (P > 0.1) between the two treatment groups. Sample size calculation: This study was not powered for efficacy comparisons between treatments; however, an a priori planned analysis included the point estimate of treatment difference and the associated two-sided 95% confidence interval (CI) in the response rates, stratified by baseline HIV-1 RNA. Intention to treat analysis: Primary efficacy analyses were intent-to-treat, missing equals failure (ITT, M=F).	75 randomised	Included: adults (≥18 years) with a screening plasma HIV-1 RNA of at least 5000 copies/ml and a CD4 cell count more than 50 cells/ml, no prior use of any approved or experimental anti-HIV drug and no NRTI, NNRTI or primary protease inhibitor genotypic resistance mutations [by International AIDS Society (IAS)-USA guidelines], normal ECG, estimated creatinine clearance (glomerular filtration rate, eGFR; Cockcroft-Gault) at least 80 ml/min, aspartate amino-transferase/ alanine aminotranferease (AST/ALT) 2.5 times or less the upper limit of normal (ULN) and total bilirubin 1.5 mg/dl or less and a negative serum pregnancy test (as applicable). Excluded: hepatitis B or C-coinfected, exhibited a new AIDS-defining condition within 30 days of screening or vaccination within 90	EVG/COBI/FTC/ TDF administered once-daily with food (n=50)	EFV/FTC/ TDF at bedtime (n=25)	48 weeks	The primary analysis objective was the efficacy of EVG/COBI/FTC/ TDF versus EFV/FTC/TDF as determined by viral suppression defined as HIV-1 RNA less than 50 copies/ml at week 24. Secondary objectives were the safety and tolerability of the regimens and viral suppression through week 48.	Gilead Sciences

	Drop out: Three participants were lost to follow-up, one withdrew consent and one participant was discontinued by the investigator due to failure to return for study visits. Setting: The study was conducted in the United States from March 2009 (screening opening and closing) through March 2010 (48-week visits)		days of study drug dosing.					
Paul E Sax et al for the GS-US-236-0102 study team. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. Lancet 2012; 379: 2439–48 David A. Wohl et al for the GS-US-236-0102 Study Team. A Randomized, Double-Blind Comparison of Single-Tablet Regimen	Design: phase 3 trial (NCT01095796; GS–US–236–0102) Randomisation: computer-generated allocation sequence with a block size of four; stratified by HIV RNA concentration at screening (≤100 000 copies per mL and >100 000 copies per mL). Allocation concealment: Investigators randomly assigned participants to one of the treatment groups by phone or internet with an interactive system (provided and managed by Bracket). Blinding: Patients and study staff involved in giving study treatment, assessing outcomes, and collecting and analysing data were masked to treatment allocation. Comparable groups at baseline: Baseline characteristics were much the same in the two treatment groups Sample size calculation: The primary end point was assessed by treatment non-inferiority of EVG/COBI/FTC/TDF compared	707 randomised	Inclusion: adults infected with HIV-1 aged at least 18 years with plasma HIV-1 RNA concentrations of 5000 copies per mL or more and no previous use of antiretroviral drugs. Participants had to have an estimated glomerular filtration rate of at least 70 mL/min and be susceptible to efavirenz, emtricitabine, and tenofovir by HIV-1 genotype (GeneSeq assay; Monogram Biosciences, South San Francisco, CA, USA) at screening. Additional inclusion criteria included aspartate and alanine aminotransferase concentrations of no more than five times the upper limit of normal; total bilirubin of no more than 25·65 µmol/L or a normal direct bilirubin,	Co-formulated elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir 300 mg (EVG/ COBI/ FTC/ TDF) once daily, plus matching placebo (n=353)	Co-formulated efavirenz 600 mg, emtricitabine 200 mg, and tenofovir 300 mg (EFV/FTC/ TDF), once daily, plus matching placebo (n=354)	192 weeks	The primary endpoint was the proportion of patients in the intention-to-treat population with viral suppression (HIV RNA <50 copies per mL) at week 48 according to snapshot analysis as defined by the US Food and Drug Administration (FDA). Other endpoints were treatment differences by subgroup, achievement and maintenance of HIV RNA	Gilead Sciences.

Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir DF Versus Single-Tablet Regimen Efavirenz/ Emtricitabine/ Tenofovir DF for Initial Treatment of HIV-1 Infection: Analysis of Week 144 Results. J Acquir Immune Defic Syndr 2014; 65 (3): e118-e121. Andrew Zolopa et al for the GS-US-236-0102 Study Team. A Randomized Double-Blind Comparison of Coformulated Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir Disoproxil Fumarate Versus Efavirenz/ Emtricitabine/ Tenofovir Disoproxil Fumarate for Initial Treatment of HIV-1 Infection: Analysis of Week 96 Results. J Acquir Immune Defic Syndr 2013; 63: 96–100	with EFV/FTC/TDF with 95% CI and with a prespecified non-inferiority margin of 12%. A sample size of 700 patients provided at least 95% power to establish non-inferiority for the percentage of patients achieving virological suppression at week 48, with assumed response rates of 79·5% in both groups, a non-inferiority margin of 12%, and a one-sided significance of 0·025. Intention to treat analysis: Intent to treat and per protocol analyses Drop out: At week 48: 22 lost to follow up, 9 non-compliant; 8 withdrew consent; 1 withdrawn by investigator; 1 pregnancy; 1 protocol violation (42/707; 6%); at week 96, a further 12 (2%) lost to follow up; at week 144 a further 20 (3%) were lost to follow up, withdrew consent or were non-compliant Setting: outpatient clinics in North America		absolute neutrophil count of at least 1000 cells per µL; at least 50 000 platelets per µL; haemoglobin concentration of at least 85 g/L; and a negative serum pregnancy test (if applicable). Positive HBsAg or hepatitis C serology was allowed. There was no screening CD4 cell count requirement Exclusion: patients with new AIDS-defining disorders or serious infections within 30 days of screening				concentration of fewer than 50 copies per mL (based on the FDA-defined time to loss of virological response algorithm), proportion of patients with HIV RNA concentrations of fewer than 50 copies per mL when classing missing as failure and missing as excluded, change in HIV RNA concentration (log10 copies per mL) from baseline, and change in CD4 cell count from baseline.	

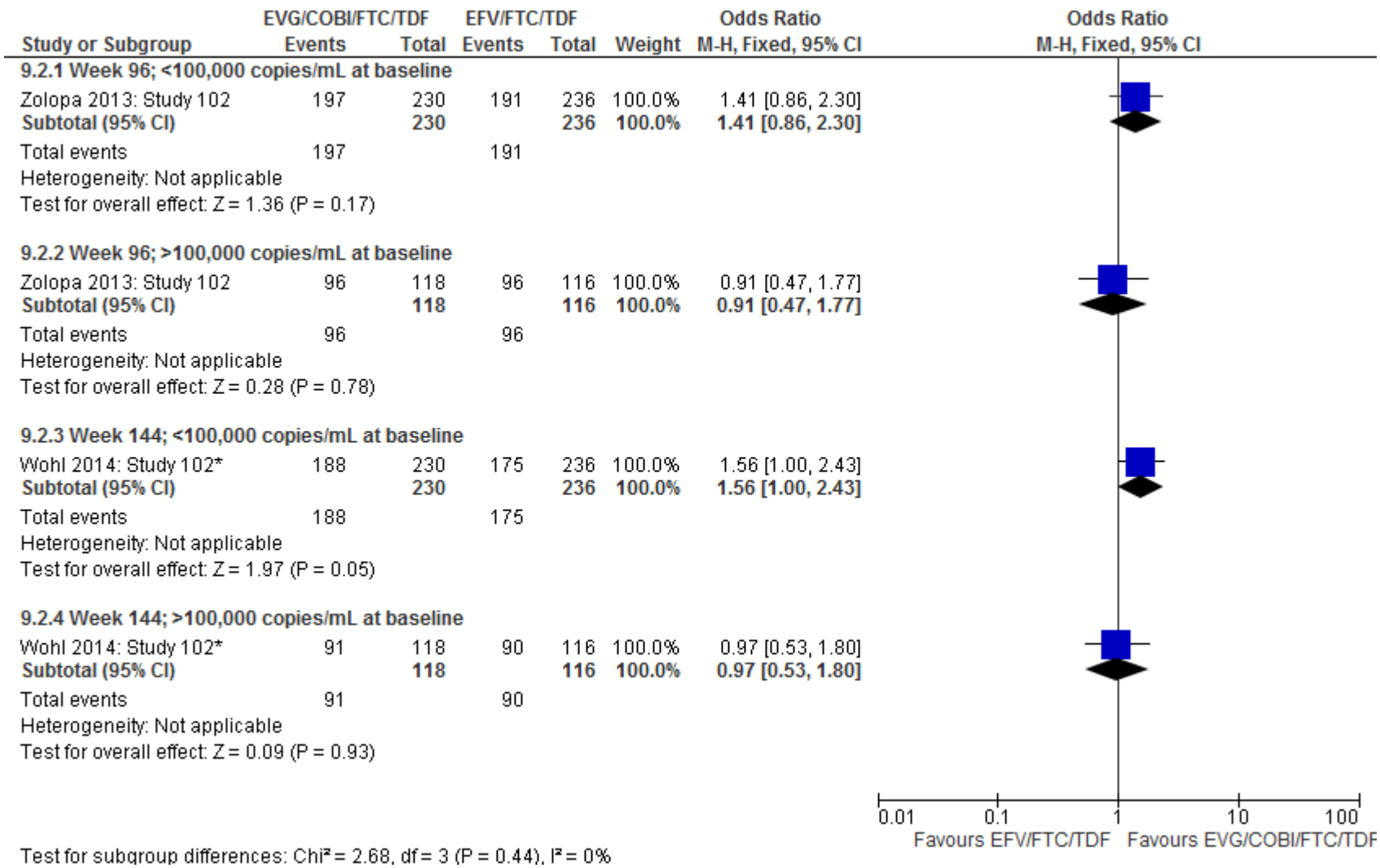
Forest plot of comparison: 9 Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate, outcome: 9.1 HIV-1 RNA less than 50 copies/ml.

Study or Subgroup	EVG/COBI/FTC/TDF Events	Total	EFV/FTC/TDF Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
9.1.1 24 weeks						
Cohen 2011: Study 104*^	43	48	19	23	100.0%	1.81 [0.44, 7.50]
Subtotal (95% CI)		**48**		**23**	**100.0%**	**1.81 [0.44, 7.50]**
Total events	43		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
9.1.2 48 weeks						
Cohen 2011: Study 104*^	43	48	19	23	6.9%	1.81 [0.44, 7.50]
Sax 2012: Study 102*	305	348	296	352	93.1%	1.34 [0.87, 2.06]
Subtotal (95% CI)		**396**		**375**	**100.0%**	**1.37 [0.91, 2.07]**
Total events	348		315			
Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%						
Test for overall effect: Z = 1.52 (P = 0.13)						
9.1.3 Week 96						
Zolopa 2013: Study 102	293	348	287	352	100.0%	1.21 [0.81, 1.79]
Subtotal (95% CI)		**348**		**352**	**100.0%**	**1.21 [0.81, 1.79]**
Total events	293		287			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						
9.1.4 Week 144						
Wohl 2014: Study 102*	279	348	265	352	100.0%	1.33 [0.93, 1.90]
Subtotal (95% CI)		**348**		**352**	**100.0%**	**1.33 [0.93, 1.90]**
Total events	279		265			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						



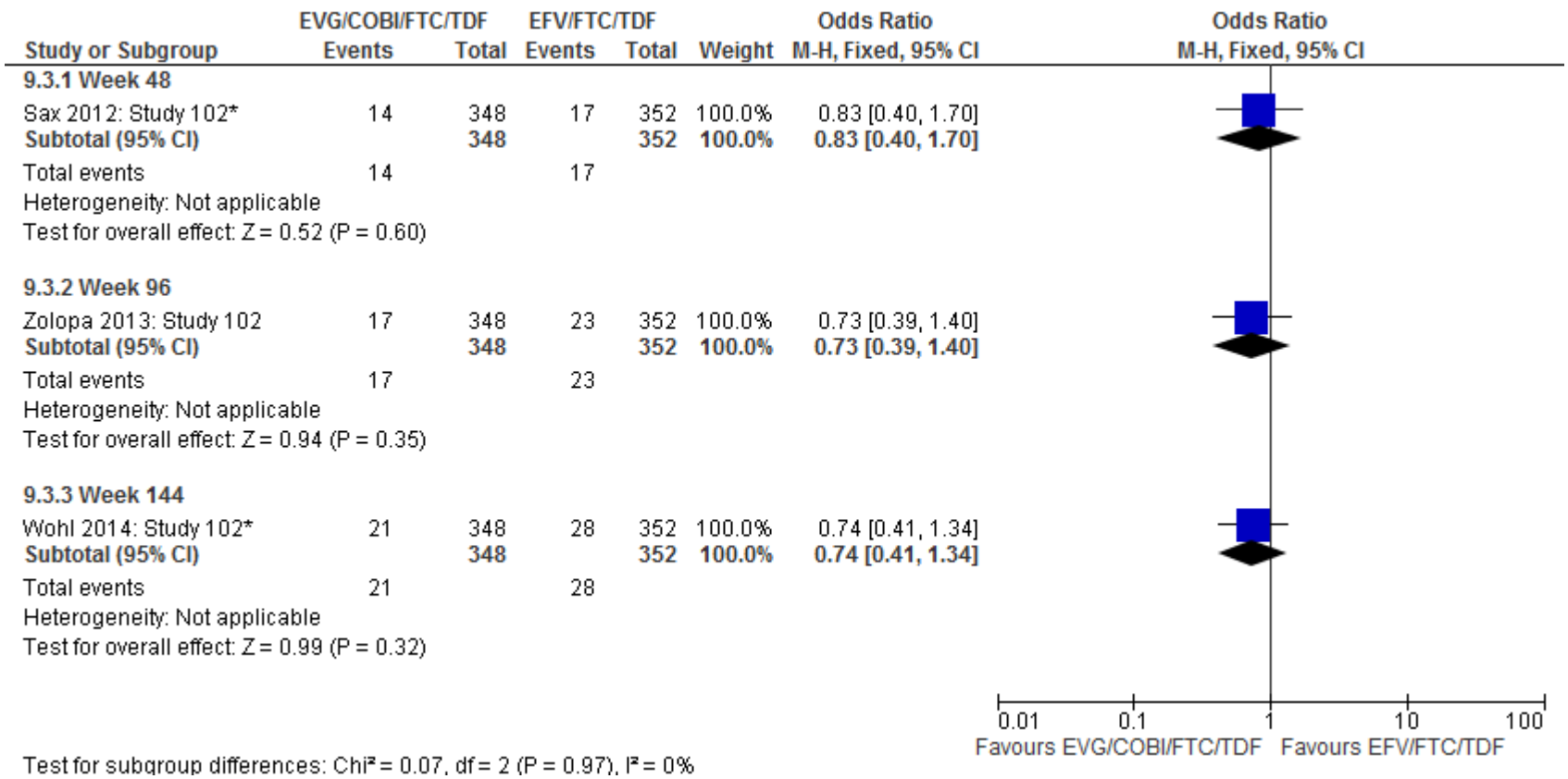
Test for subgroup differences: Chi² = 0.42, df = 3 (P = 0.94), I² = 0%

Forest plot of comparison: 9 Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate, outcome: 9.2 HIV-1 RNA less than 50 copies/ml; subgroups.



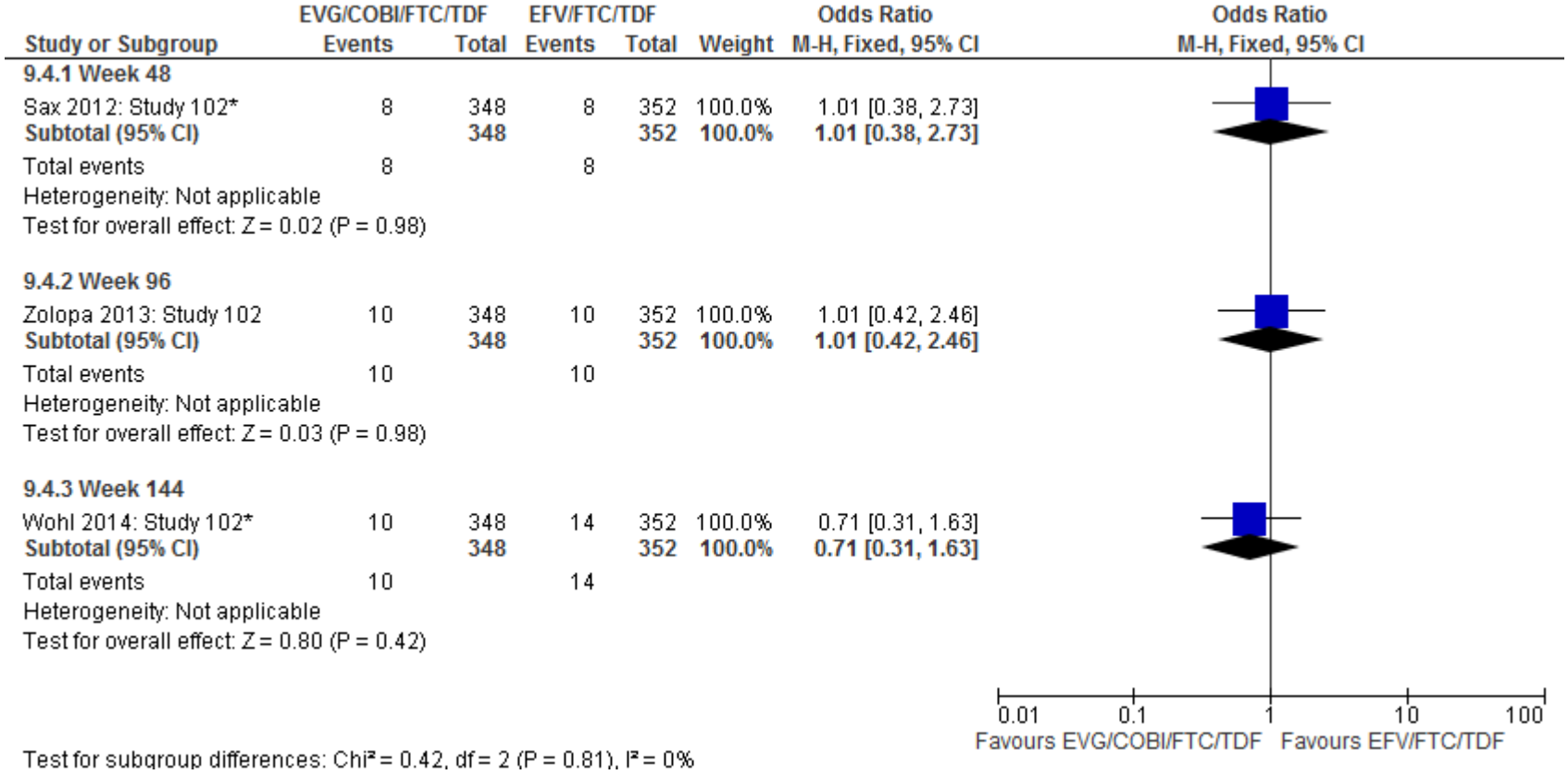
Test for subgroup differences: $Chi^2 = 2.68$, df = 3 (P = 0.44), $I^2 = 0\%$

Forest plot of comparison: 9 Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate, outcome: 9.3 Virological failure.



Subgroups by < or >100,000 copies/mL at baseline not available.

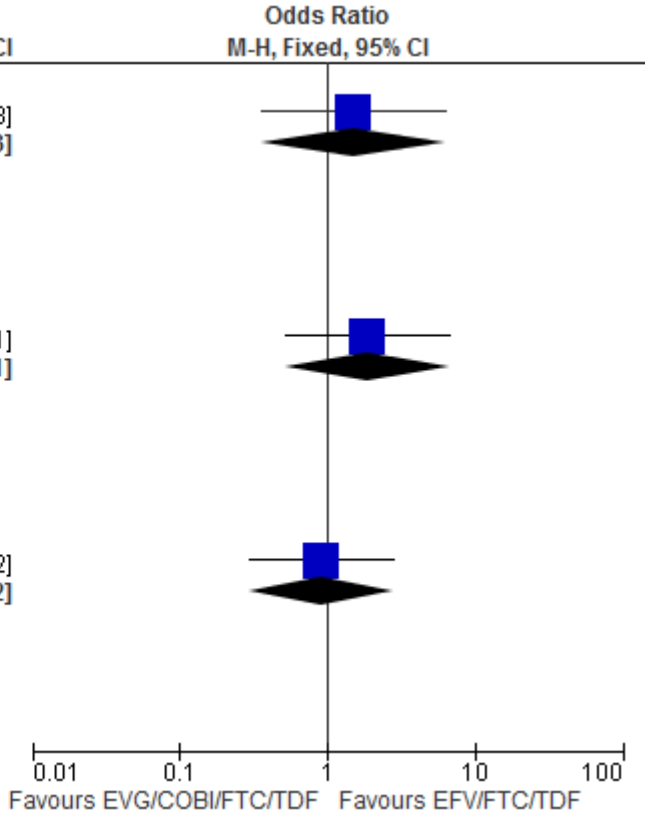
Forest plot of comparison: 9 Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate, outcome: 9.4 Resistance (% total population).



Forest plot of comparison: 9 Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate, outcome: 9.5 Resistance (% of those with virological failure).

Study or Subgroup	EVG/COBI/FTC/TDF Events	Total	EFV/FTC/TDF Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
9.5.1 Week 48						
Sax 2012: Study 102*	8	14	8	17	100.0%	1.50 [0.36, 6.23]
Subtotal (95% CI)		**14**		**17**	**100.0%**	**1.50 [0.36, 6.23]**
Total events	8		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.58)						
9.5.2 Week 96						
Zolopa 2013: Study 102	10	17	10	23	100.0%	1.86 [0.52, 6.61]
Subtotal (95% CI)		**17**		**23**	**100.0%**	**1.86 [0.52, 6.61]**
Total events	10		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						
9.5.3 Week 144						
Wohl 2014: Study 102*	10	21	14	28	100.0%	0.91 [0.29, 2.82]
Subtotal (95% CI)		**21**		**28**	**100.0%**	**0.91 [0.29, 2.82]**
Total events	10		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.87)						

Test for subgroup differences: Chi² = 0.72, df = 2 (P = 0.70), I² = 0%



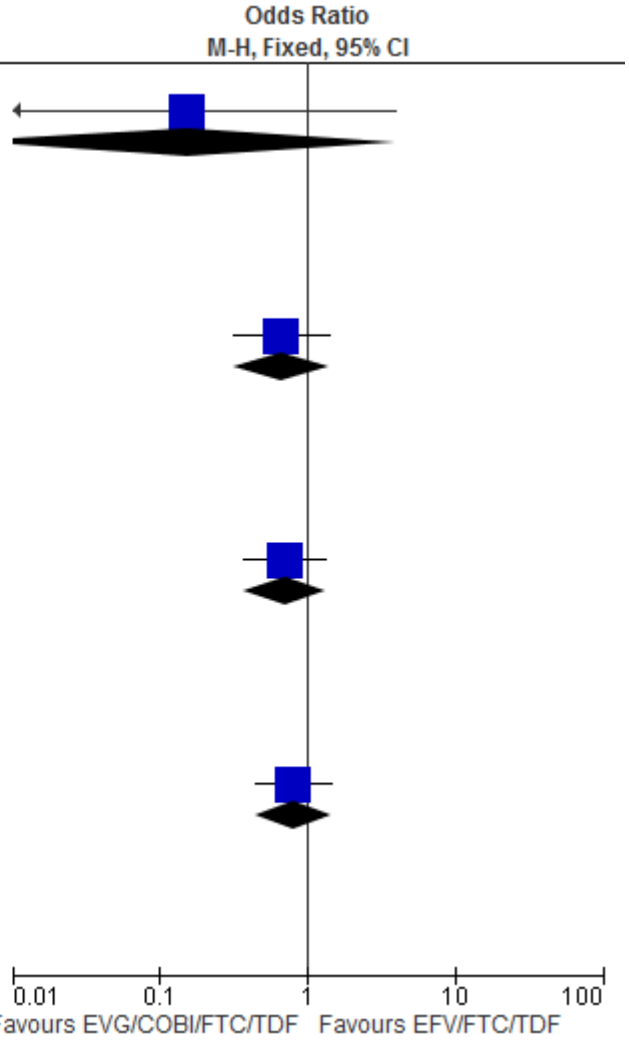
At week 48 (Sax 2012; Study 102): Of patients who received treatment, 31 (4%) met the criteria for resistance testing, 14/348 (4%) in the EVG/COBI/FTC/TDF group and 17/352 (5%) in the EFV/FTC/TDF group. Of the 14 patients in the EVG/COBI/FTC/TDF group, eight had resistance mutations. These eight patients had nucleoside reverse transcriptase inhibitor resistance mutations (five had Met184Val/Ile [M184V/I] only, three had Met184Val/Ile and Lys65Arg [K65R]). Seven of the eight patients also had integrase resistance mutations (mainly Glu92Gln [E92Q]). Of the 17 patients in the EFV/FTC/TDF group analysed for resistance, eight developed resistance to one or more components of EFV/FTC/TDF; the most common resistance profile was the Lys103Asn (K103N) mutation (seven patients, five with Lys103Asn, two with Lys103Asn, Met184Val, and Lys65Arg).

At week 96 (Zolopa 2013; Study 102): Development of resistance to 1 or more components of the regimens was infrequent through week 96. Forty patients met virologic criteria for resistance testing [EVG/COBI/FTC/TDF 17 (4.9%) vs EFV/FTC/TDF 23 (6.5%)]. Ten of 17 EVG/COBI/FTC/TDF patients had emergent resistance mutations. Nine of the 10 patients had integrase resistance mutations (primarily E92Q). All 10 patients had NRTI resistance mutations (6 with M184V/I alone, and 4 with M184V/I and K65R). Ten of 23 EFV/FTC/TDF patients had emergent resistance mutations; the most common resistance mutation was K103N mutation (9 patients) with or without the combination of M184V/I and K65R (3 patients). Only 2 patients in each group developed resistance mutations after the first 48 weeks and no new resistance patterns or unique mutations emerged between weeks 48 and 96.

Week 144 (Wohl 2014; Study 102): Development of resistance to one or more components of the regimens was infrequent. Through week 144, 49 patients met criteria for resistance testing (21 EVG/COBI/FTC/TDF vs 28 EFV/FTC/TDF). Overall, resistance mutations emerged in 10 of 21 patients in the EVG/COBI/FTC/TDF group; 9 patients in the integrase gene (primarily E92Q) and all 10 patients in reverse transcriptase (6 with M184V/I, and 4 with M184V/I and K65R). In the EVG/COBI/FTC/TDF group, no patient developed resistance after week 96. In the EFV/FTC/TDF group, resistance mutations in reverse transcriptase emerged in 14 of 28 patients; the most common resistance mutation was K103N (n = 13) with M184V/I (n = 1) or with M184V/I and K65R (n = 3).

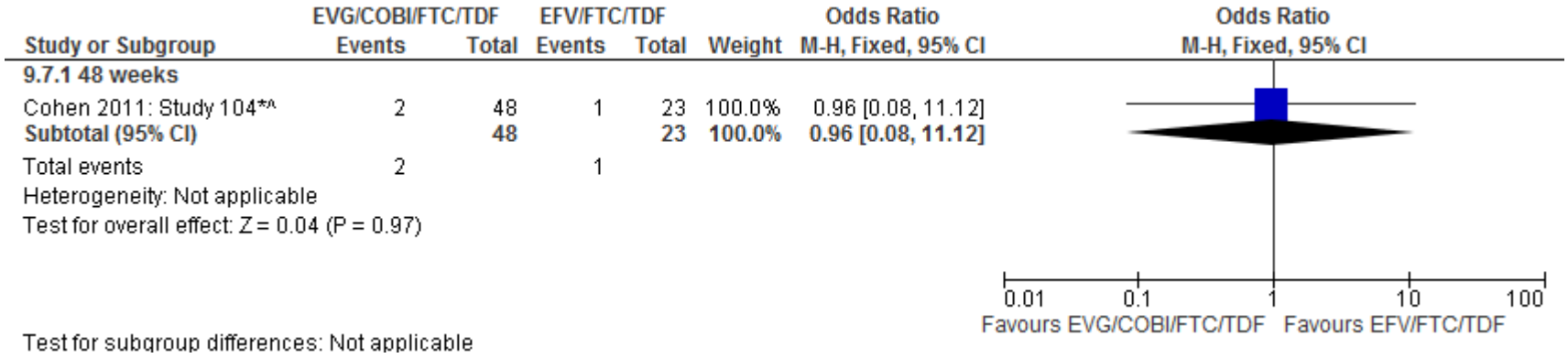
Forest plot of comparison: 9 Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate, outcome: 9.6 Discontinued due to adverse event.

Study or Subgroup	EVG/COBI/FTC/TDF Events	Total	EFV/FTC/TDF Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
9.6.1 24 weeks						
Cohen 2011: Study 104*^	0	48	1	23	100.0%	0.15 [0.01, 3.95]
Subtotal (95% CI)		**48**		**23**	**100.0%**	**0.15 [0.01, 3.95]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.13 (P = 0.26)						
9.6.2 Week 48						
Sax 2012: Study 102*	12	348	18	352	100.0%	0.66 [0.31, 1.40]
Subtotal (95% CI)		**348**		**352**	**100.0%**	**0.66 [0.31, 1.40]**
Total events	12		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						
9.6.3 Week 96						
Zolopa 2013: Study 102	17	348	24	352	100.0%	0.70 [0.37, 1.33]
Subtotal (95% CI)		**348**		**352**	**100.0%**	**0.70 [0.37, 1.33]**
Total events	17		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						
9.6.4 Week 144						
Wohl 2014: Study 102*	21	348	26	352	100.0%	0.81 [0.44, 1.46]
Subtotal (95% CI)		**348**		**352**	**100.0%**	**0.81 [0.44, 1.46]**
Total events	21		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						

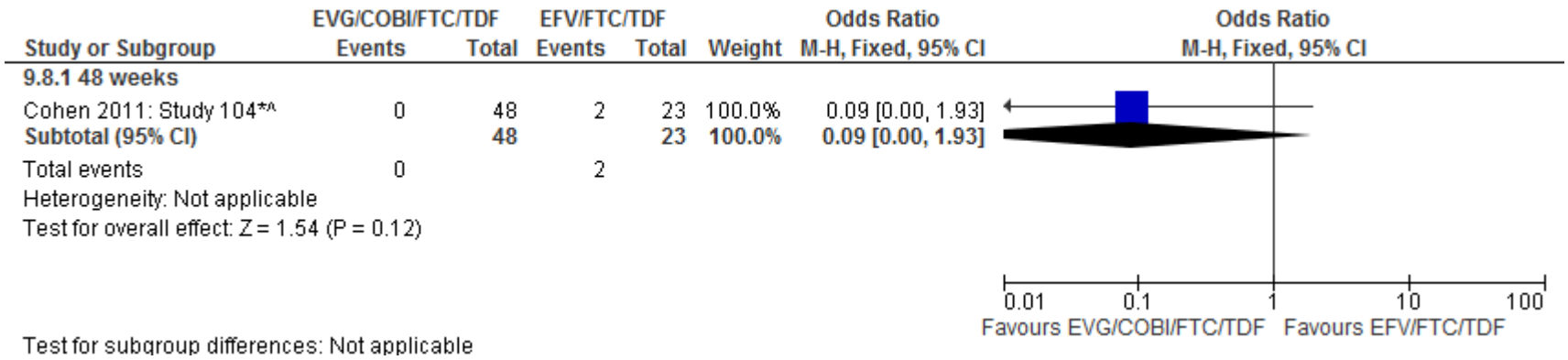


Test for subgroup differences: Chi² = 1.05, df = 3 (P = 0.79), I² = 0%

Forest plot of comparison: 9 Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate, outcome: 9.7 Grade 3 and/or grade 4 treatment-emergent adverse events (clinical).



Forest plot of comparison: 9 Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate, outcome: 9.8 Grade 3 and/or grade 4 treatment-emergent adverse events (laboratory).



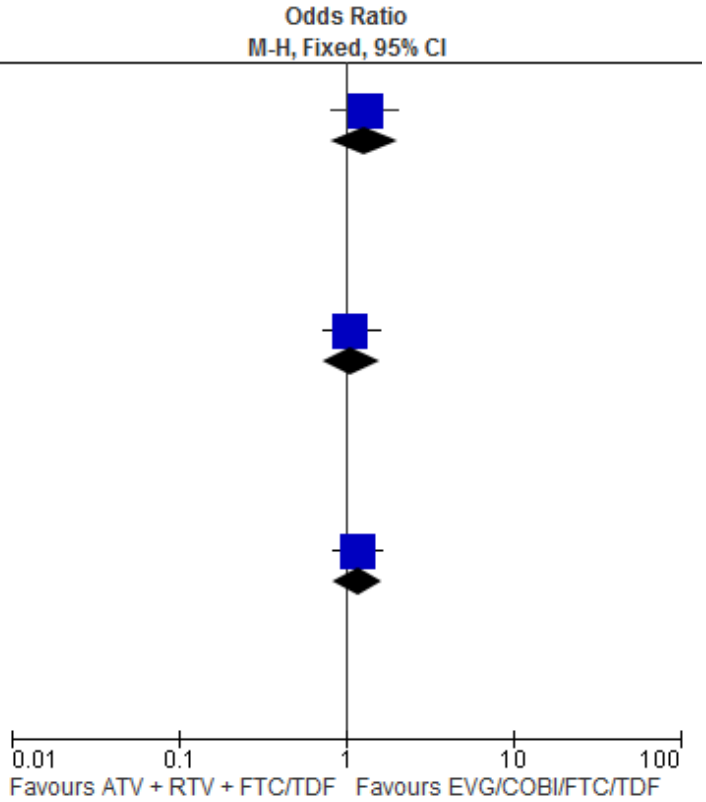
No data on Grade 3-4 rash, AST/ALT, CNS events or diarrhoea.

10 Elvitegravir, cobicistat, emtricitabine, and tenofovir versus ritonavir-boosted atazanavir plus emtricitabine/ tenofovir

Study 103 included in previous guidelines.

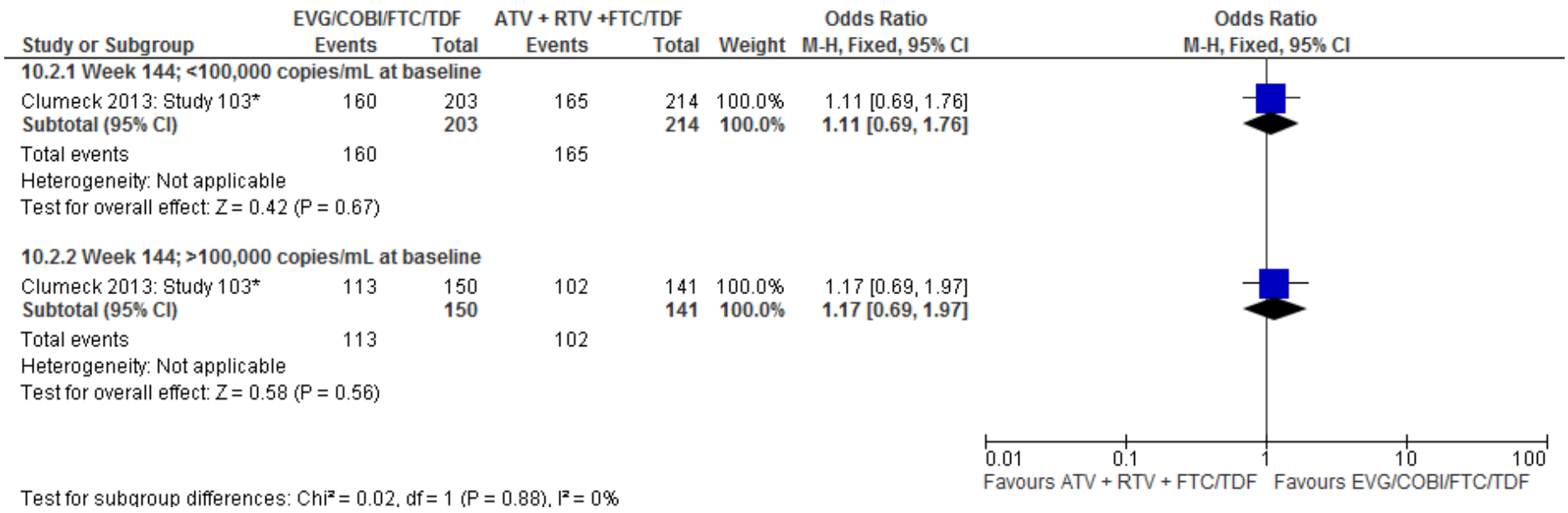
Forest plot of comparison: 10 Elvitegravir, cobicistat, emtricitabine, and tenofovir versus ritonavir-boosted atazanavir plus emtricitabine/ tenofovir, outcome: 10.1 HIV-1 RNA <50 copies/mL.

Study or Subgroup	EVG/COBI/FTC/TDF Events	Total	ATV + RTV +FTC/TDF Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
10.1.1 Week 48						
DeJesus 2012: Study 103*	316	353	308	355	100.0%	1.30 [0.82, 2.06]
Subtotal (95% CI)		**353**		**355**	**100.0%**	**1.30 [0.82, 2.06]**
Total events	316		308			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.13 (P = 0.26)						
10.1.2 Week 96						
Rockstroh 2013: Study 103	294	353	292	355	100.0%	1.08 [0.73, 1.59]
Subtotal (95% CI)		**353**		**355**	**100.0%**	**1.08 [0.73, 1.59]**
Total events	294		292			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.36 (P = 0.72)						
10.1.3 144 weeks						
Clumeck 2013: Study 103*	274	353	265	355	100.0%	1.18 [0.83, 1.67]
Subtotal (95% CI)		**353**		**355**	**100.0%**	**1.18 [0.83, 1.67]**
Total events	274		265			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						



Test for subgroup differences: Chi² = 0.39, df = 2 (P = 0.82), I² = 0%

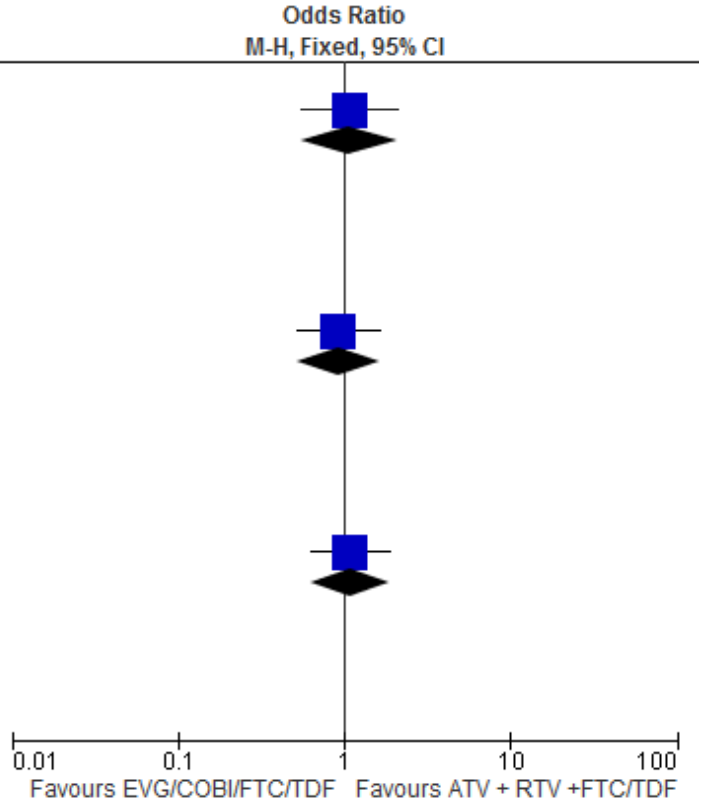
Forest plot of comparison: 10 Elvitegravir, cobicistat, emtricitabine, and tenofovir versus ritonavir-boosted atazanavir plus emtricitabine/ tenofovir, outcome: 10.2 HIV-1 RNA <50 copies/mL; subgroups.



Forest plot of comparison: 10 Elvitegravir, cobicistat, emtricitabine, and tenofovir versus ritonavir-boosted atazanavir plus emtricitabine/ tenofovir, outcome: 10.3 Virological failure.

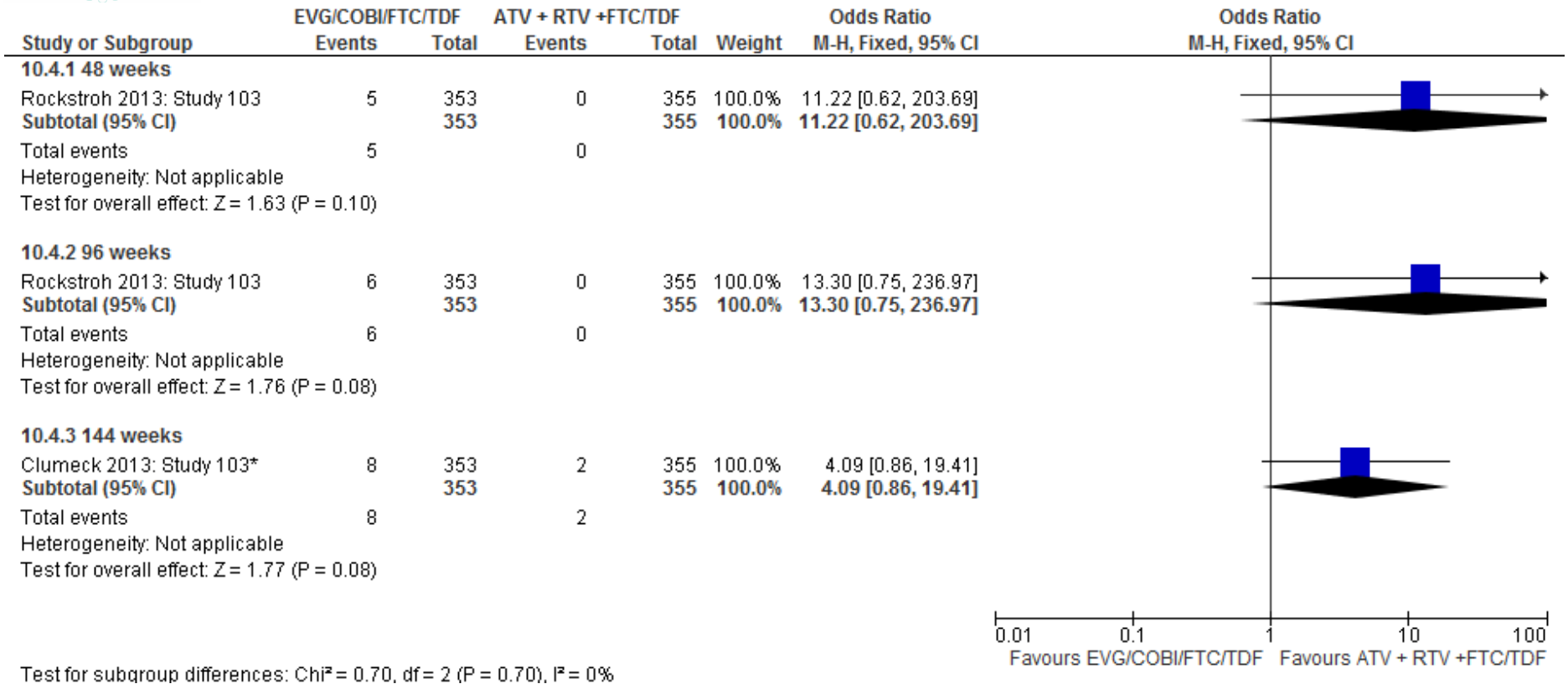
Study or Subgroup	EVG/COBI/FTC/TDF Events	Total	ATV + RTV +FTC/TDF Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
10.3.1 48 weeks						
Rockstroh 2013: Study 103	19	353	18	355	100.0%	1.07 [0.55, 2.07]
Subtotal (95% CI)		**353**		**355**	**100.0%**	**1.07 [0.55, 2.07]**
Total events	19		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.19 (P = 0.85)						
10.3.2 96 weeks						
Rockstroh 2013: Study 103	24	353	26	355	100.0%	0.92 [0.52, 1.64]
Subtotal (95% CI)		**353**		**355**	**100.0%**	**0.92 [0.52, 1.64]**
Total events	24		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
10.3.3 144 weeks						
Clumeck 2013: Study 103*	28	353	26	355	100.0%	1.09 [0.63, 1.90]
Subtotal (95% CI)		**353**		**355**	**100.0%**	**1.09 [0.63, 1.90]**
Total events	28		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.30 (P = 0.76)						

Test for subgroup differences: Chi² = 0.19, df = 2 (P = 0.91), I² = 0%



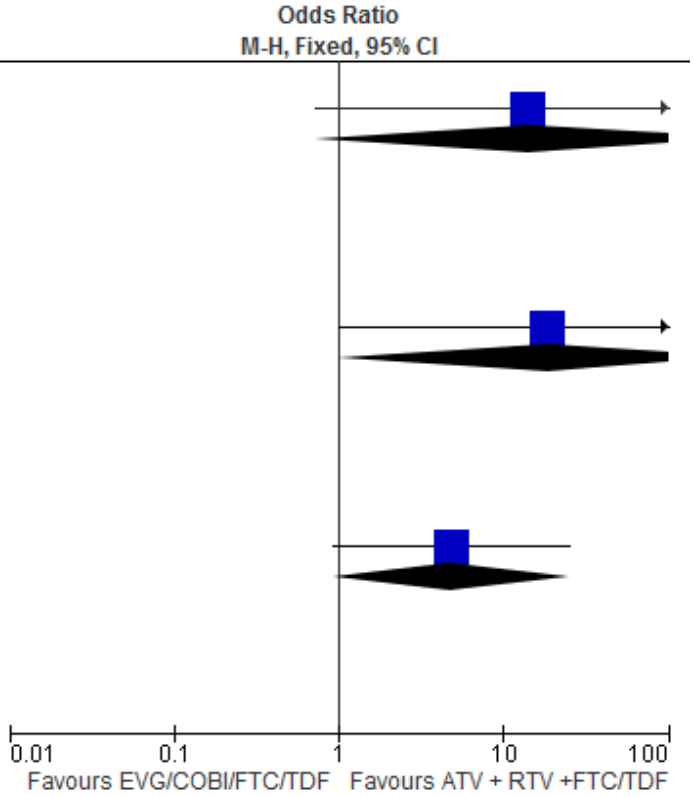
Subgroup analysis by < or > 100,00 copies at baseline not available.

Forest plot of comparison: 10 Elvitegravir, cobicistat, emtricitabine, and tenofovir versus ritonavir-boosted atazanavir plus emtricitabine/ tenofovir, outcome: 10.4 Resistance (% total population).



Forest plot of comparison: 10 Elvitegravir, cobicistat, emtricitabine, and tenofovir versus ritonavir-boosted atazanavir plus emtricitabine/ tenofovir, outcome: 10.5 Resistance (% of those with virological failure).

Study or Subgroup	EVG/COBI/FTC/TDF Events	Total	ATV + RTV +FTC/TDF Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
10.5.1 48 weeks						
Rockstroh 2013: Study 103	5	19	0	18	100.0%	14.03 [0.72, 275.08]
Subtotal (95% CI)		**19**		**18**	**100.0%**	**14.03 [0.72, 275.08]**
Total events	5		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.74 (P = 0.08)						
10.5.2 96 weeks						
Rockstroh 2013: Study 103	6	24	0	26	100.0%	18.62 [0.99, 351.22]
Subtotal (95% CI)		**24**		**26**	**100.0%**	**18.62 [0.99, 351.22]**
Total events	6		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.95 (P = 0.05)						
10.5.3 144 weeks						
Clumeck 2013: Study 103*	8	28	2	26	100.0%	4.80 [0.91, 25.23]
Subtotal (95% CI)		**28**		**26**	**100.0%**	**4.80 [0.91, 25.23]**
Total events	8		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.85 (P = 0.06)						

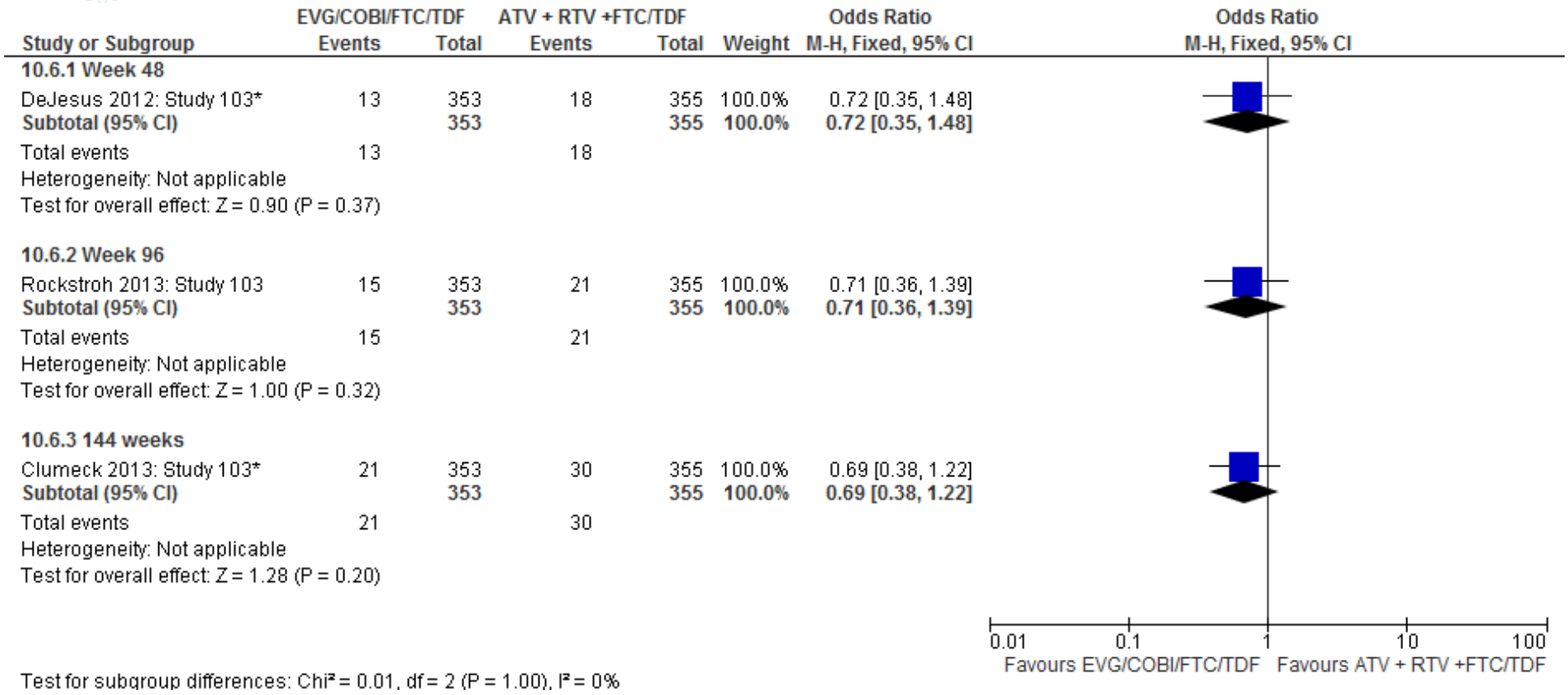


Test for subgroup differences: Chi² = 0.82, df = 2 (P = 0.67), I² = 0%

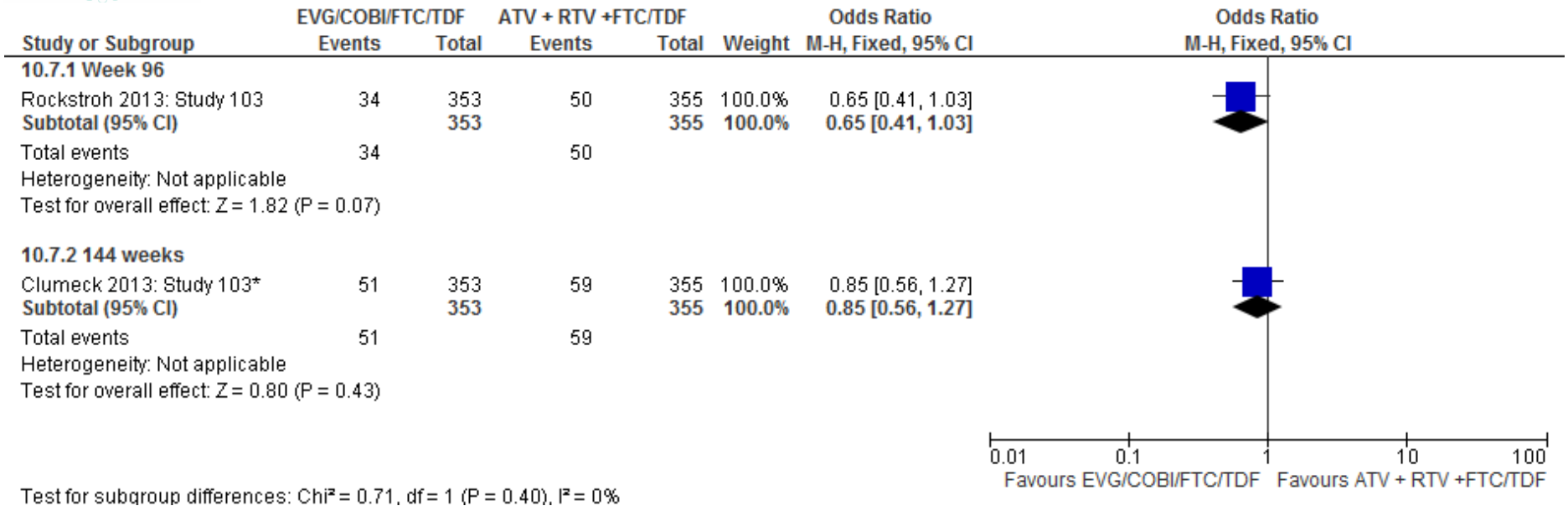
Development of resistance to one or more component of the EVG/COBI/FTC/TDF regimen was infrequent. Overall, 6 (1.7%) subjects in the EVG/COBI/FTC/TDF group failed with emergent resistance mutations vs no subjects in the ATV/RTV + FTC/TDF group. Of the 6 subjects with resistance to EVG/COBI/FTC/TDF, 5 occurred during the first 48 weeks and 1 occurred during the second 48 weeks of treatment, which failed with M184V but no integrase resistance.

Cumulatively, 8 (2.3%) subjects in the EVG/COBI/FTC/TDF group failed with emergent resistance mutations vs 2 (0.6%) subjects in the ATV + RTV + FTC/TDF group through week 144. In the EVG/COBI/FTC/TDF group, emergent resistance through week 144 was comprised of T66I (n = 1), E92Q (n = 2), Q148R (n = 2), N155H (n = 2), and T97A (n = 1) in integrase and M184V/I (n = 7) and K65R (n = 1) in reverse transcriptase. In the ATV + RTV + FTC/TDF group, 2 patients had emergent M184V/I in reverse transcriptase.

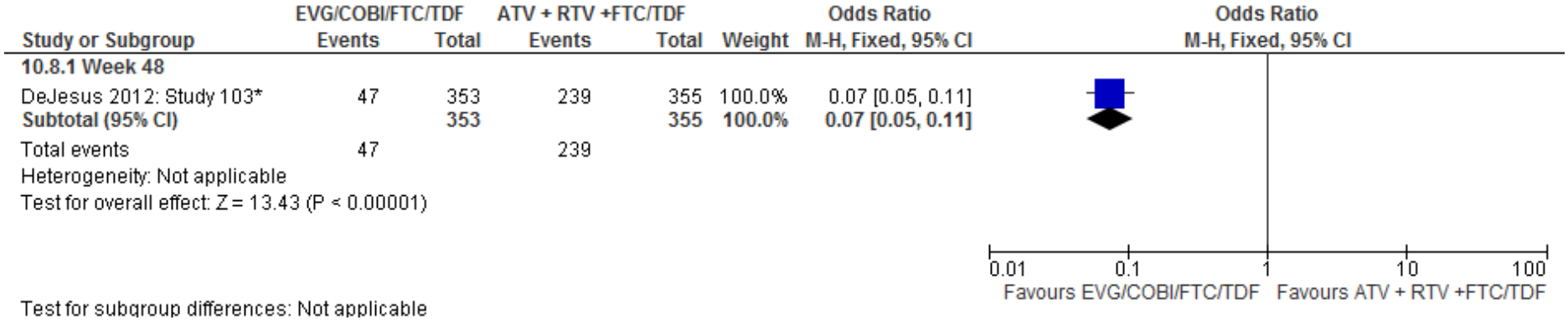
Forest plot of comparison: 10 Elvitegravir, cobicistat, emtricitabine, and tenofovir versus ritonavir-boosted atazanavir plus emtricitabine/ tenofovir, outcome: 10.6 Discontinued due to AE.



Forest plot of comparison: 10 Elvitegravir, cobicistat, emtricitabine, and tenofovir versus ritonavir-boosted atazanavir plus emtricitabine/ tenofovir, outcome: 10.7 Serious AEs (not stated if clinical or laboratory).



Forest plot of comparison: 10 Elvitegravir, cobicistat, emtricitabine, and tenofovir versus ritonavir-boosted atazanavir plus emtricitabine/ tenofovir, outcome: 10.8 Grade 3 or 4 laboratory abnormalities.

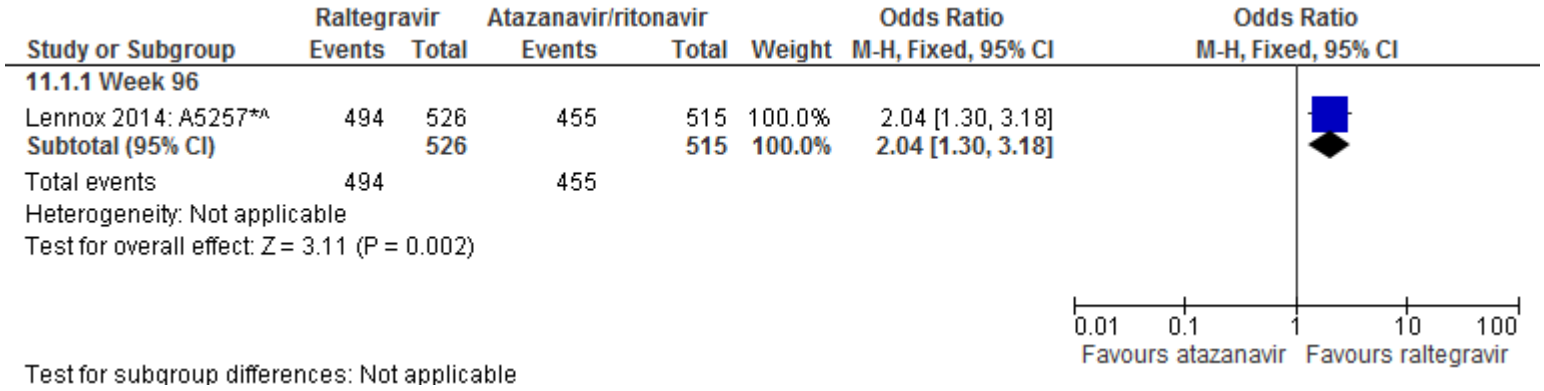


No data on Grade 3-4 rash, AST/ALT, CNS events or diarrhoea.

11 Raltegravir vs. atazanavir/ritonavir, all with tenofovir/emtricitabine

The Lennox 2014 paper (study A5257) is a three-arm trial (raltegravir vs. atazanavir vs. darunavir) and is described in the table in section 2 (darunavir vs. atazanavir).

Forest plot of comparison: 11 Raltegravir vs. atazanavir/ritonavir, all with tenofovir/emtricitabine, outcome: 11.1 Virological response.



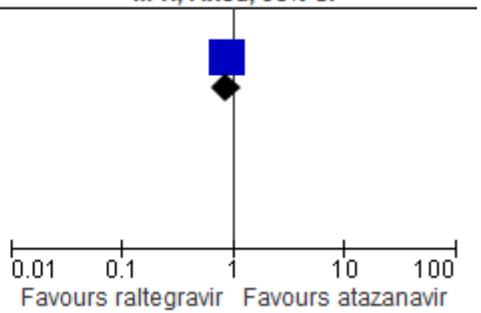
Lennox 2014 did not report response by baseline load < or > 100,000 copies/mL.

Forest plot of comparison: 11 Raltegravir vs. atazanavir/ritonavir, all with tenofovir/emtricitabine, outcome: 11.2 Virological failure.

Study or Subgroup	Raltegravir Events	Total	Atazanavir/ritonavir Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
11.2.1 Week 96						
Lennox 2014: A5257*^	85	603	95	605	100.0%	0.88 [0.64, 1.21]
Subtotal (95% CI)		**603**		**605**	**100.0%**	**0.88 [0.64, 1.21]**
Total events	85		95			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.78 (P = 0.43)



Test for subgroup differences: Not applicable

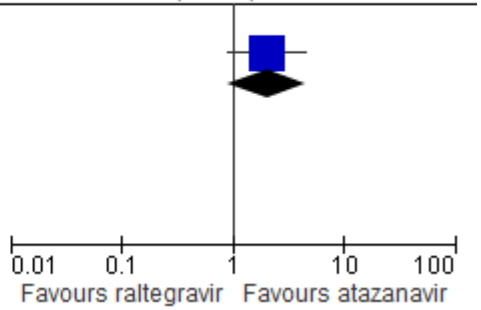
Lennox 2014 did not report failure by baseline load < or > 100,000 copies/mL.

Forest plot of comparison: 11 Raltegravir vs. atazanavir/ritonavir, all with tenofovir/emtricitabine, outcome: 11.3 Resistance (% of total population).

Study or Subgroup	Raltegravir Events	Total	Atazanavir/ritonavir Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
11.3.1 Week 96						
Lennox 2014: A5257*^	18	603	9	605	100.0%	2.04 [0.91, 4.57]
Subtotal (95% CI)		**603**		**605**	**100.0%**	**2.04 [0.91, 4.57]**
Total events	18		9			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.73 (P = 0.08)



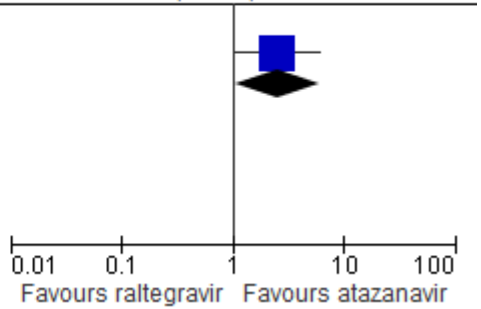
Test for subgroup differences: Not applicable

Forest plot of comparison: 11 Raltegravir vs. atazanavir/ritonavir, all with tenofovir/emtricitabine, outcome: 11.4 Resistance (% of virological failure).

Study or Subgroup	Raltegravir Events	Total	Atazanavir/ritonavir Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
11.4.1 Week 96						
Lennox 2014: A5257*^	18	85	9	95	100.0%	2.57 [1.08, 6.08]
Subtotal (95% CI)		**85**		**95**	**100.0%**	**2.57 [1.08, 6.08]**
Total events	18		9			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.14 (P = 0.03)



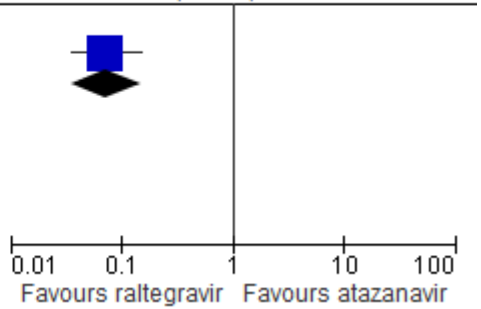
Test for subgroup differences: Not applicable

Forest plot of comparison: 11 Raltegravir vs. atazanavir/ritonavir, all with tenofovir/emtricitabine, outcome: 11.5 Discontinued due to adverse events.

Study or Subgroup	Raltegravir Events	Total	Atazanavir/ritonavir Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
11.5.1 Week 96						
Lennox 2014: A5257*^	8	603	95	605	100.0%	0.07 [0.03, 0.15]
Subtotal (95% CI)		**603**		**605**	**100.0%**	**0.07 [0.03, 0.15]**
Total events	8		95			

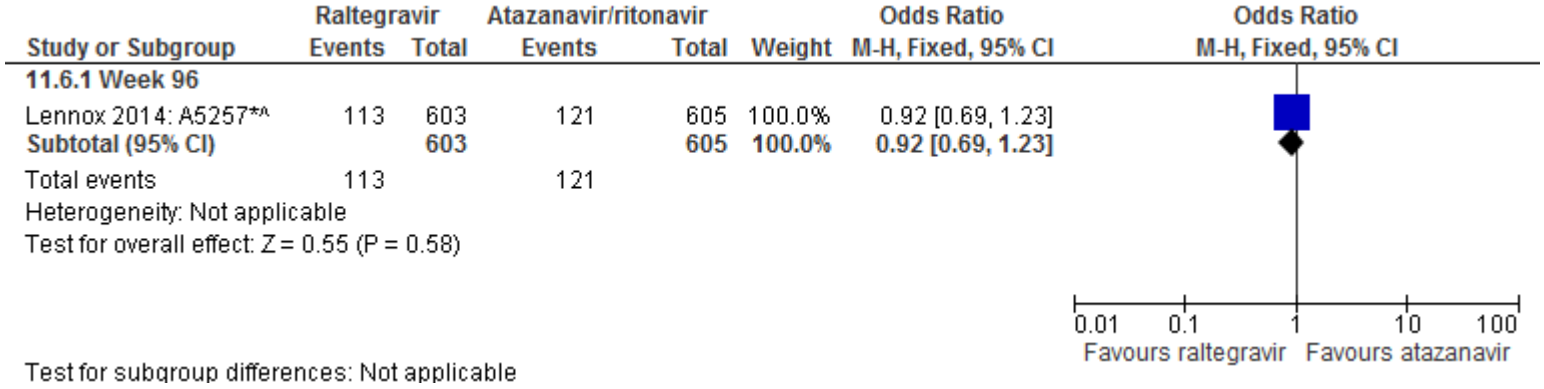
Heterogeneity: Not applicable

Test for overall effect: Z = 7.05 (P < 0.00001)

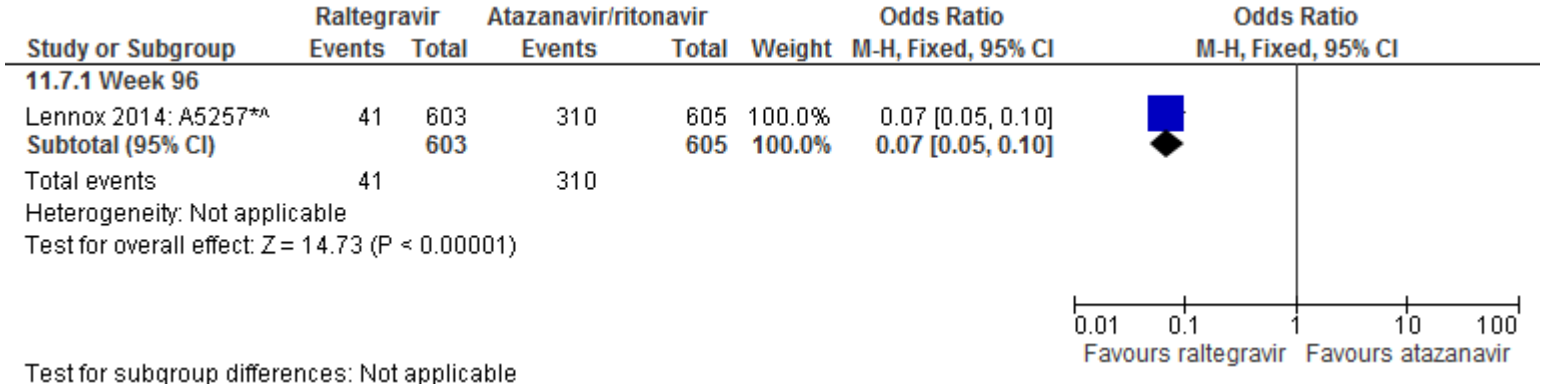


Test for subgroup differences: Not applicable

Forest plot of comparison: 11 Raltegravir vs. atazanavir/ritonavir, all with tenofovir/emtricitabine, outcome: 11.6 Grade 3 or 4 clinical adverse events.



Forest plot of comparison: 11 Raltegravir vs. atazanavir/ritonavir, all with tenofovir/emtricitabine, outcome: 11.7 Grade 3 or 4 laboratory adverse events.

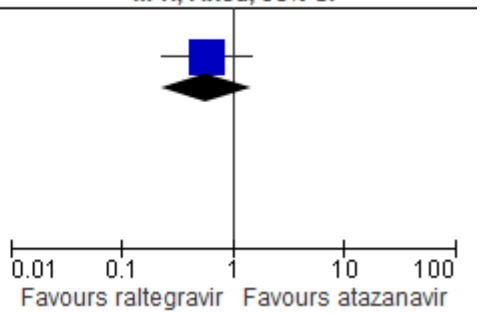


Forest plot of comparison: 11 Raltegravir vs. atazanavir/ritonavir, all with tenofovir/emtricitabine, outcome: 11.8 Grade 3 or 4 headache.

Study or Subgroup	Raltegravir Events	Total	Atazanavir/ritonavir Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
11.8.1 Week 96						
Lennox 2014: A5257*^	7	603	12	605	100.0%	0.58 [0.23, 1.48]
Subtotal (95% CI)		**603**		**605**	**100.0%**	**0.58 [0.23, 1.48]**
Total events	7		12			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.14 (P = 0.26)



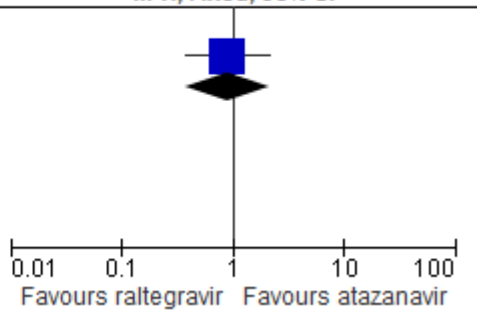
Test for subgroup differences: Not applicable

Forest plot of comparison: 11 Raltegravir vs. atazanavir/ritonavir, all with tenofovir/emtricitabine, outcome: 11.9 Grade 3 or 4 diarrhoea.

Study or Subgroup	Raltegravir Events	Total	Atazanavir/ritonavir Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
11.9.1 Week 96						
Lennox 2014: A5257*^	10	603	11	605	100.0%	0.91 [0.38, 2.16]
Subtotal (95% CI)		**603**		**605**	**100.0%**	**0.91 [0.38, 2.16]**
Total events	10		11			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.21 (P = 0.83)



Test for subgroup differences: Not applicable

12 Raltegravir vs. Darunavir/ritonavir, all with tenofovir/emtricitabine

The Lennox 2014 paper (study A5257) is a three-arm trial (raltegravir vs. atazanavir vs. darunavir) and is described in the table in section 2 (darunavir vs. atazanavir).

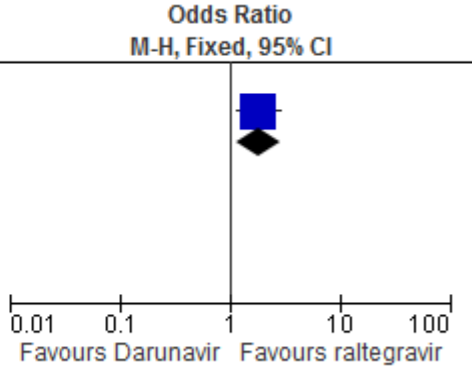
Forest plot of comparison: 12 Raltegravir vs. darunavir/ritonavir, all with tenofovir/emtricitabine, outcome: 12.1 Virological response.

	Raltegravir		Darunavir/ritonavir			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
12.1.1 Week 96						
Lennox 2014: A5257*^	494	526	463	518	100.0%	1.83 [1.16, 2.89]
Subtotal (95% CI)		**526**		**518**	**100.0%**	**1.83 [1.16, 2.89]**
Total events	494		463			

Heterogeneity: Not applicable

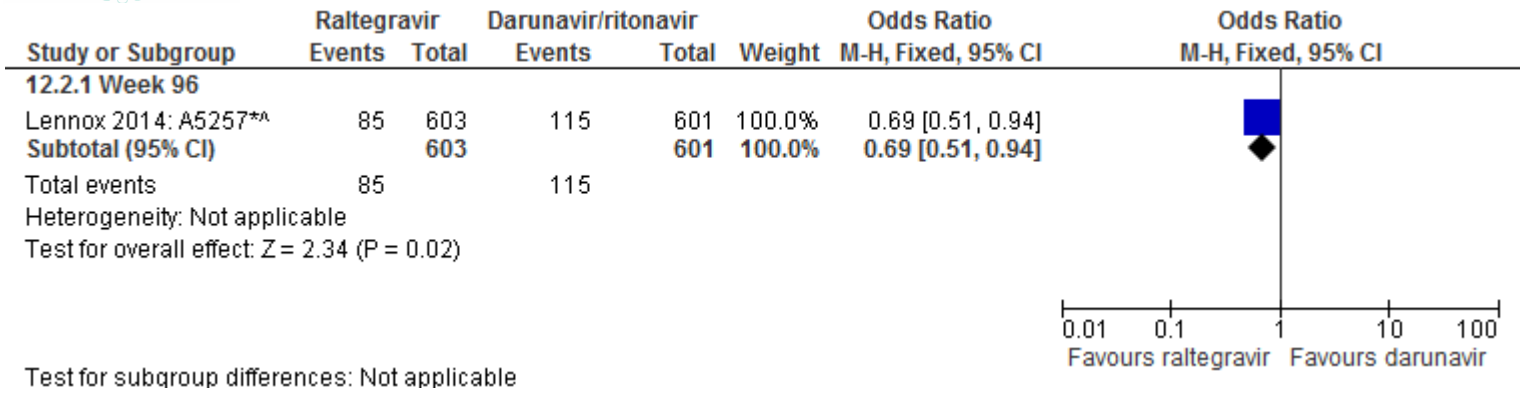
Test for overall effect: Z = 2.62 (P = 0.009)

Test for subgroup differences: Not applicable



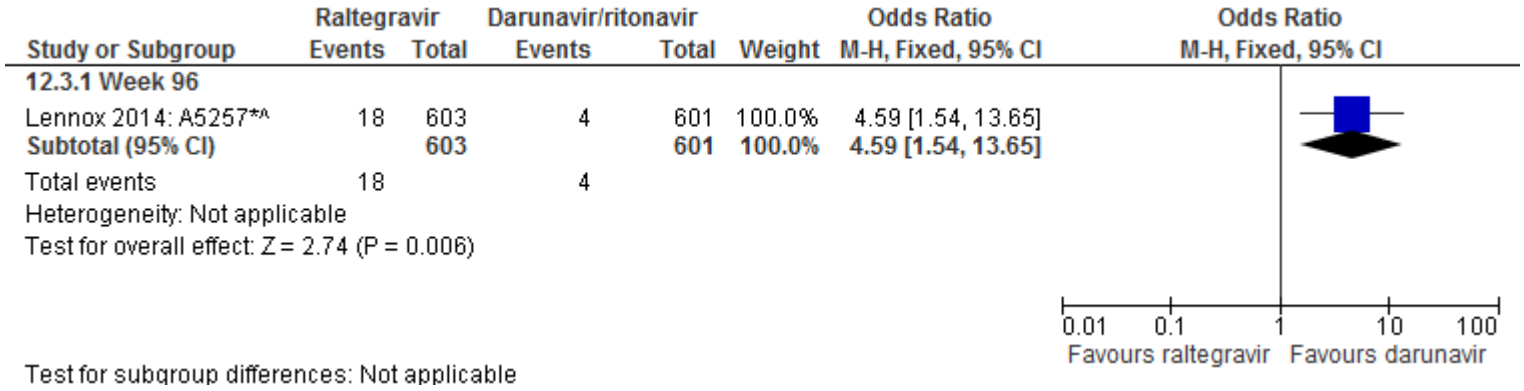
Lennox 2014 did not report response by baseline load < or > 100,000 copies/mL.

Forest plot of comparison: 12 Raltegravir vs. darunavir/ritonavir, all with tenofovir/emtricitabine, outcome: 12.2 Virological failure.

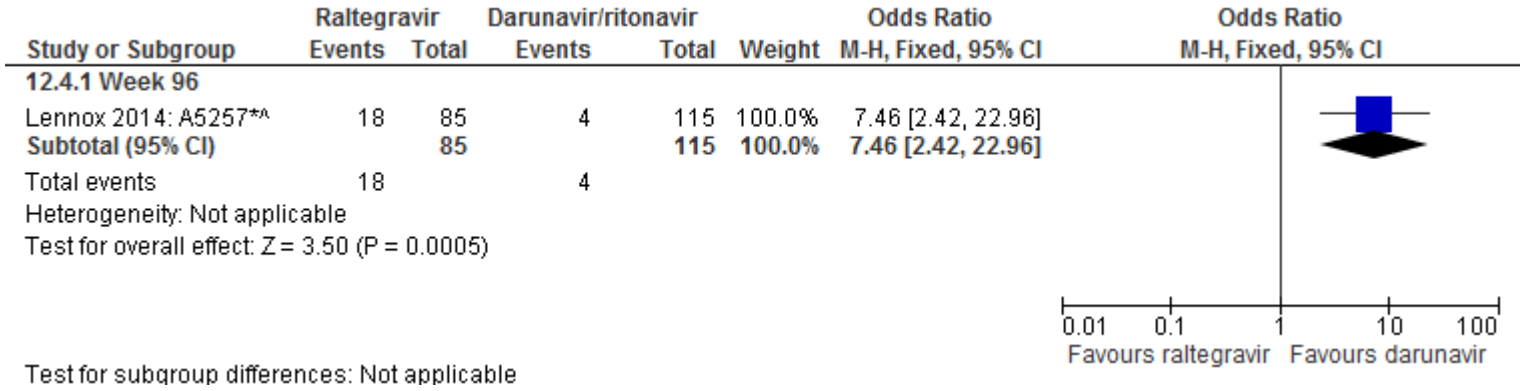


Lennox 2014 did not report failure by baseline load < or > 100,000 copies/mL.

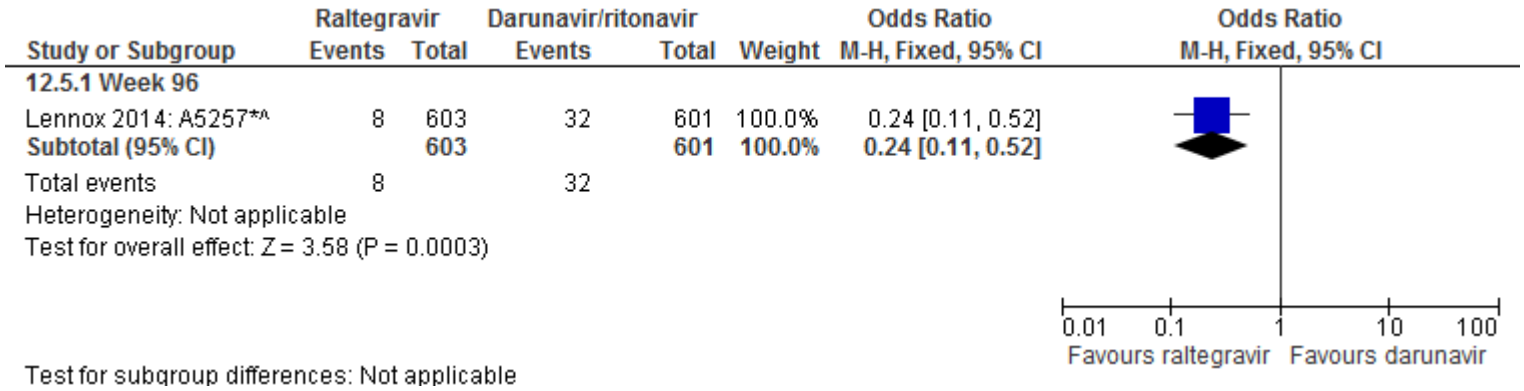
Forest plot of comparison: 12 Raltegravir vs. darunavir/ritonavir, all with tenofovir/emtricitabine, outcome: 12.3 Resistance (% total population).



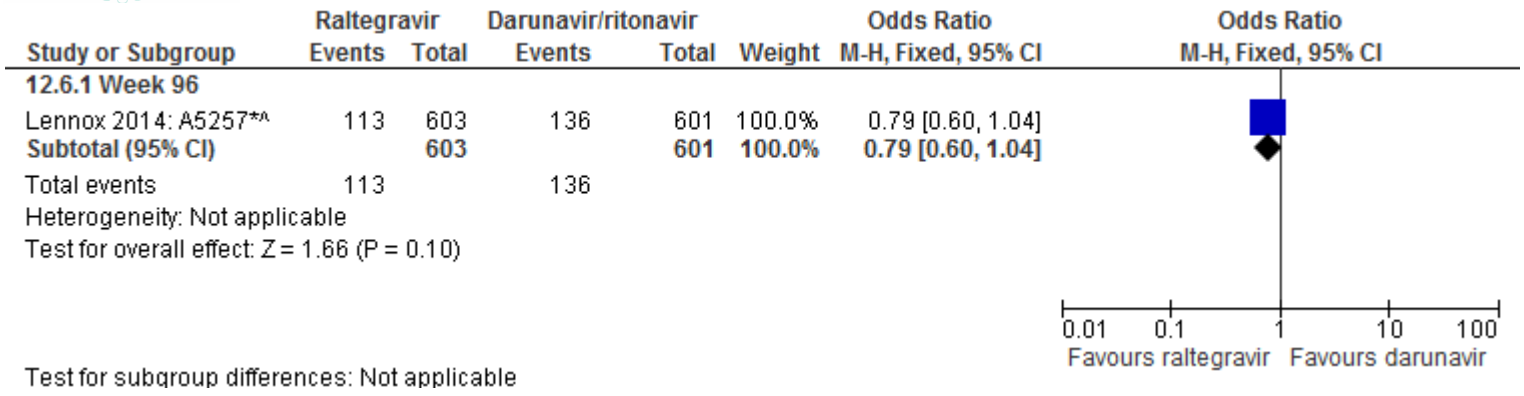
Forest plot of comparison: 12 Raltegravir vs. darunavir/ritonavir, all with tenofovir/emtricitabine, outcome: 12.4 Resistance (% virological failure).



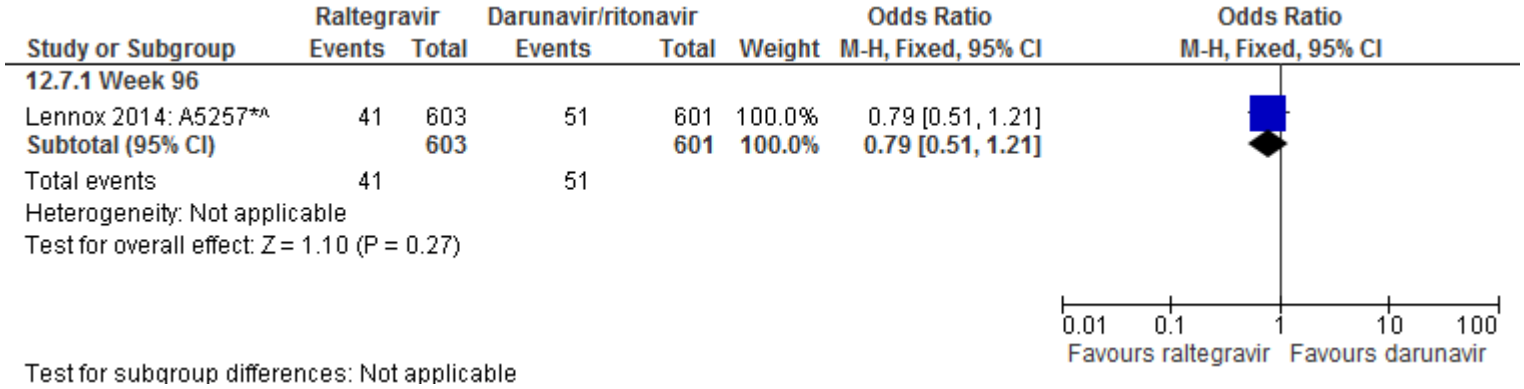
Forest plot of comparison: 12 Raltegravir vs. darunavir/ritonavir, all with tenofovir/emtricitabine, outcome: 12.5 Discontinued due to adverse events.



Forest plot of comparison: 12 Raltegravir vs. darunavir/ritonavir, all with tenofovir/emtricitabine, outcome: 12.6 Grade 3 or 4 clinical adverse events.



Forest plot of comparison: 12 Raltegravir vs. darunavir/ritonavir, all with tenofovir/emtricitabine, outcome: 12.7 Grade 3 or 4 laboratory adverse events.

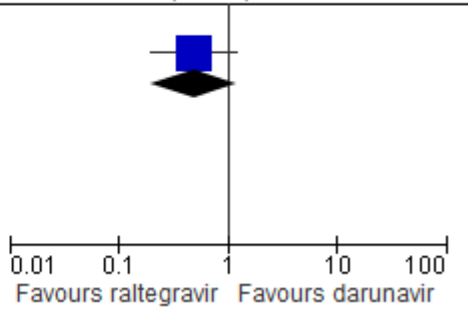


Forest plot of comparison: 12 Raltegravir vs. darunavir/ritonavir, all with tenofovir/emtricitabine, outcome: 12.8 Grade 3 or 4 headache.

Study or Subgroup	Raltegravir Events	Total	Darunavir/ritonavir Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
12.8.1 Week 96						
Lennox 2014: A5257*^	7	603	14	601	100.0%	0.49 [0.20, 1.23]
Subtotal (95% CI)		**603**		**601**	**100.0%**	**0.49 [0.20, 1.23]**
Total events	7		14			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.52 (P = 0.13)



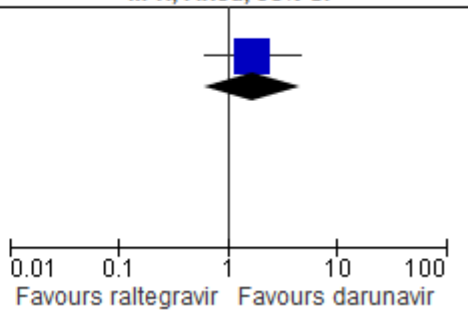
Test for subgroup differences: Not applicable

Forest plot of comparison: 12 Raltegravir vs. darunavir/ritonavir, all with tenofovir/emtricitabine, outcome: 12.9 Grade 3 or 4 diarrhoea.

Study or Subgroup	Raltegravir Events	Total	Darunavir/ritonavir Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
12.9.1 Week 96						
Lennox 2014: A5257*^	10	603	6	601	100.0%	1.67 [0.60, 4.63]
Subtotal (95% CI)		**603**		**601**	**100.0%**	**1.67 [0.60, 4.63]**
Total events	10		6			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.99 (P = 0.32)



Test for subgroup differences: Not applicable

Important comparison only if new data since 2012 guidelines

Comparisons:

13 ABC/3TC/EFV versus TDF/FTC/EFV

14 Atazanavir-ritonavir + ABC/3TC or TDF/FTC versus efavirenz + ABC/3TC or TDF/FTC

15 Atazanavir/r + 2 NRTI versus efavirenz + 2 NRTI

16 Raltegravir once daily + tenofovir-emtricitabine versus raltegravir twice daily + tenofovir-emtricitabine

17 Raltegravir + tenofovir/ emtricitabine versus efavirenz + tenofovir/ emtricitabine

18 Raltegravir + tenofovir/ lamivudine versus efavirenz + tenofovir/ lamivudine

19 Rilpivirine + emtricitabine/tenofovir versus efavirenz + emtricitabine/tenofovir

Key outcomes:

a) Efficacy HIV RNA <50 copies/mL; subgroups by < or >100,000 copies/mL at baseline

b) Virological failure; subgroups by < or >100,000 copies/mL at baseline

c) Resistance: i) as a proportion of all randomised patients

ii) as a proportion of those with virological failure

d) Discontinuation due to adverse events

e) Grade 3-4 adverse events (clinical)

f) Grade 3-4 adverse events (laboratory)

g) Grade 3-4 rash

h) Grade 3-4 raised AST or ALT

i) Grade 3-4 CNS events

j) Grade 3-4 diarrhoea

Forest plots

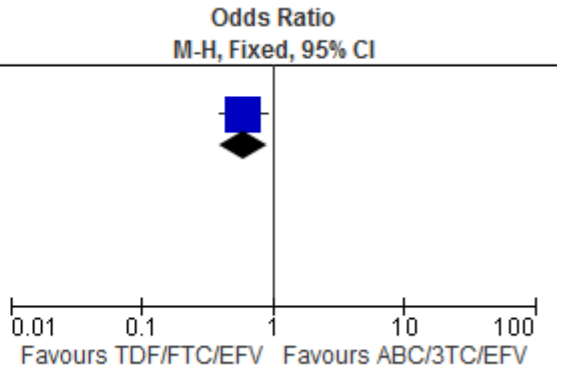
13 ABC/3TC/EFV versus TDF/FTC/EFV

No new data for the key outcomes (Clotet 2012 published after the cut-off date but re-analysis of ASSERT trial already included).

Information included from previous guideline (studies ACTG 5202 [efavirenz subgroup; Sax 2011] and ASSERT [Post 2010]; see previous guideline for evidence tables):

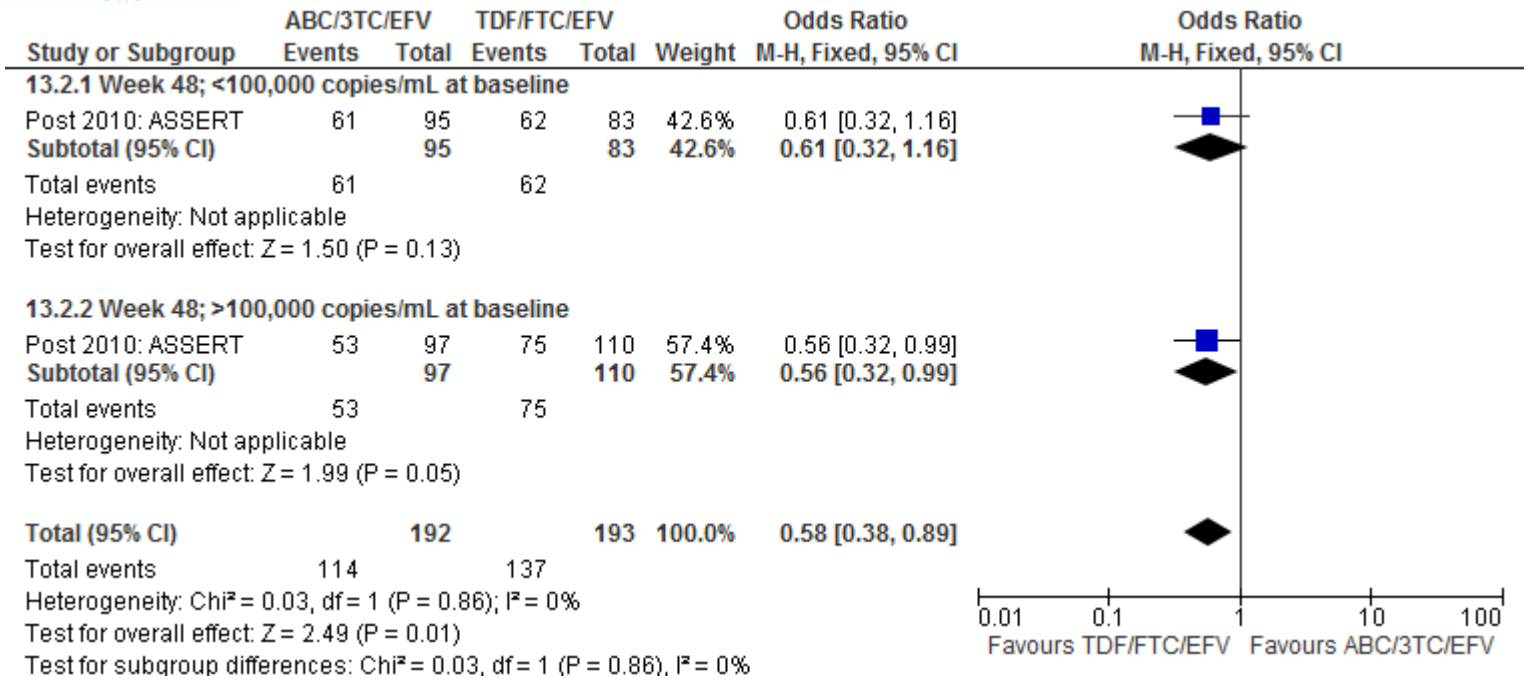
Forest plot of comparison: 13 ABC/3TC/EFV versus TDF/FTC/EFV, outcome: 13.1 HIV-1 RNA < 50 copies/mL.

	ABC/3TC/EFV		TDF/FTC/EFV			Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
13.1.1 Week 48						
Post 2010: ASSERT	114	192	137	193	100.0%	0.60 [0.39, 0.91]
Subtotal (95% CI)		**192**		**193**	**100.0%**	**0.60 [0.39, 0.91]**
Total events	114		137			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.38 (P = 0.02)						

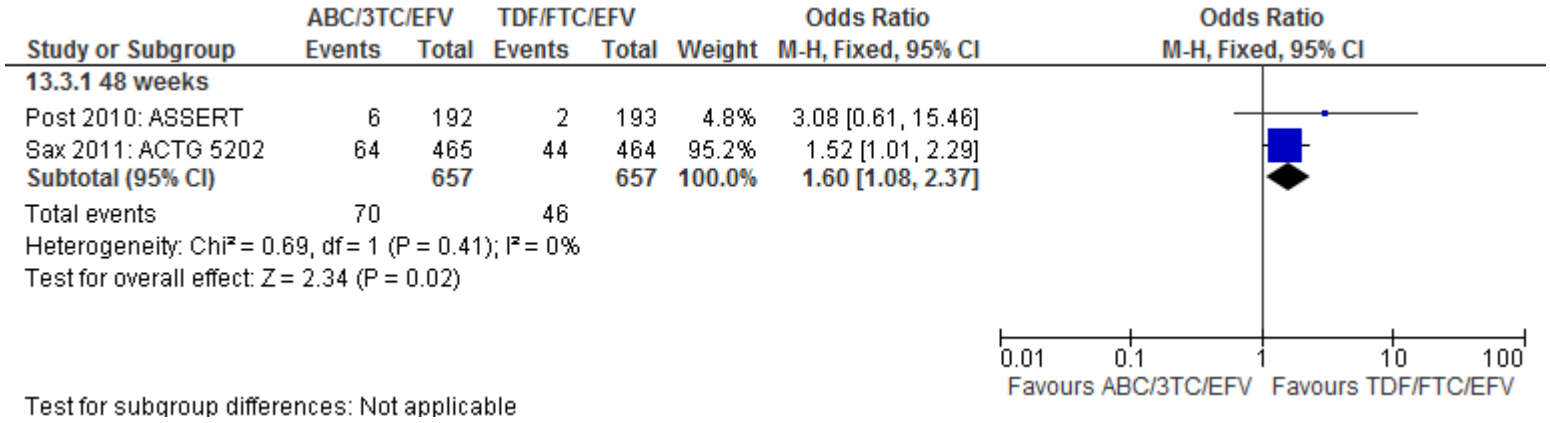


Test for subgroup differences: Not applicable

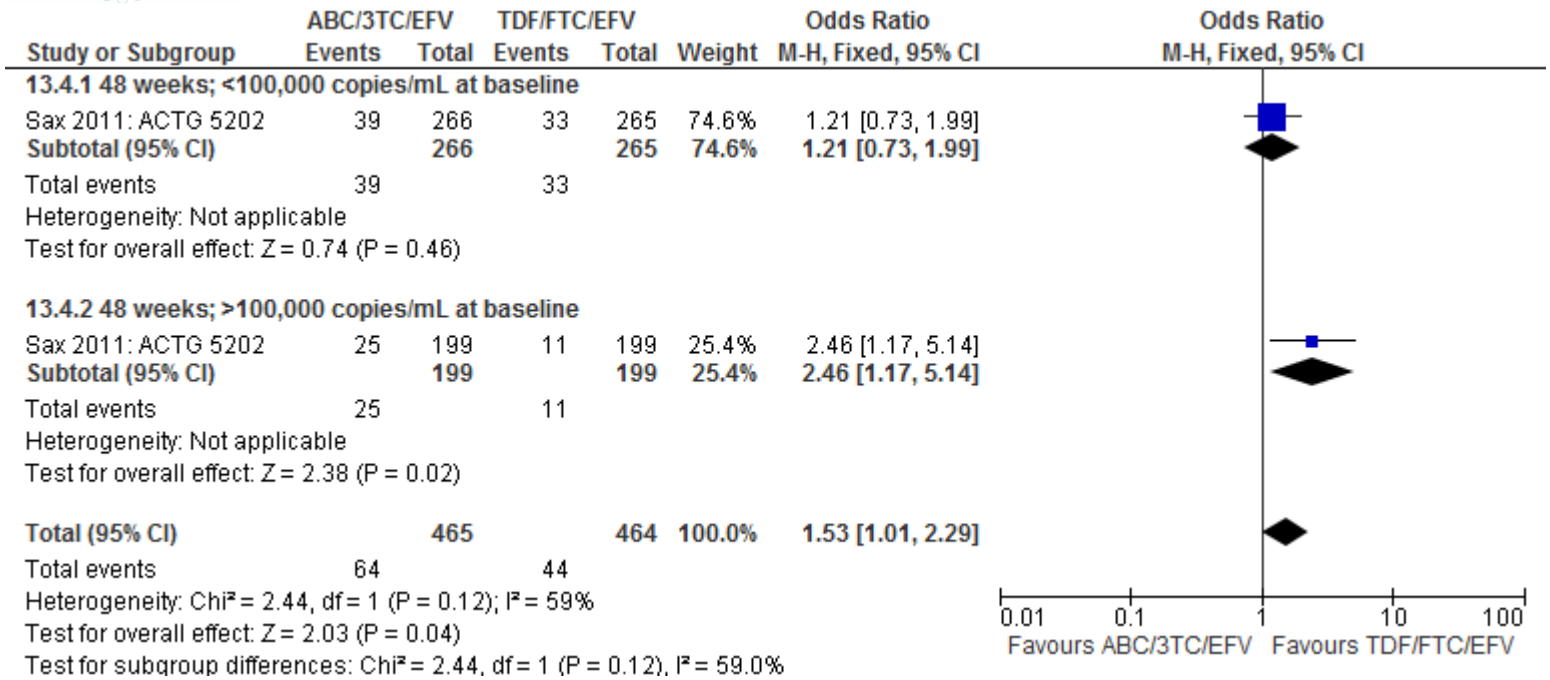
Forest plot of comparison: 13 ABC/3TC/EFV versus TDF/FTC/EFV, outcome: 13.2 HIV-1 RNA < 50 copies/mL; subgroups.



Forest plot of comparison: 13 ABC/3TC/EFV versus TDF/FTC/EFV, outcome: 13.3 Virological failure.



Forest plot of comparison: 13 ABC/3TC/EFV versus TDF/FTC/EFV, outcome: 13.4 Virological failure; subgroups.

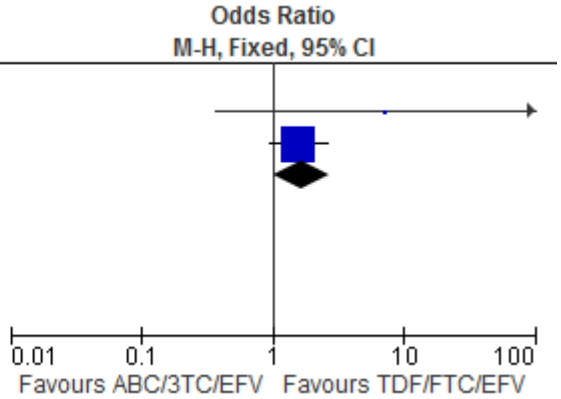


Forest plot of comparison: 13 ABC/3TC/EFV versus TDF/FTC/EFV, outcome: 13.5 Resistance (% of total population).

Study or Subgroup	ABC/3TC/EFV Events	Total	TDF/FTC/EFV Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
13.5.1 Week 48						
Post 2010: ASSERT	3	192	0	193	2.0%	7.15 [0.37, 139.32]
Sax 2011: ACTG 5202	41	461	27	461	98.0%	1.57 [0.95, 2.60]
Subtotal (95% CI)		**653**		**654**	**100.0%**	**1.68 [1.03, 2.75]**
Total events	44		27			

Heterogeneity: Chi² = 0.98, df = 1 (P = 0.32); I² = 0%

Test for overall effect: Z = 2.06 (P = 0.04)



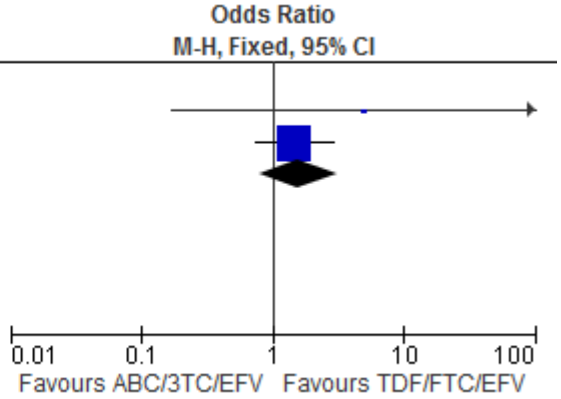
Test for subgroup differences: Not applicable

Forest plot of comparison: 13 ABC/3TC/EFV versus TDF/FTC/EFV, outcome: 13.6 Resistance (% patients with virological failure).

Study or Subgroup	ABC/3TC/EFV Events	Total	TDF/FTC/EFV Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
13.6.1 Week 48						
Post 2010: ASSERT	3	6	0	2	2.6%	5.00 [0.17, 146.64]
Sax 2011: ACTG 5202	41	72	27	57	97.4%	1.47 [0.73, 2.95]
Subtotal (95% CI)		**78**		**59**	**100.0%**	**1.56 [0.79, 3.08]**
Total events	44		27			

Heterogeneity: Chi² = 0.48, df = 1 (P = 0.49); I² = 0%

Test for overall effect: Z = 1.29 (P = 0.20)



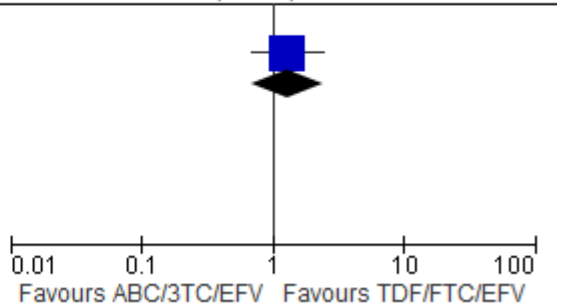
Test for subgroup differences: Not applicable

Forest plot of comparison: 13 ABC/3TC/EFV versus TDF/FTC/EFV, outcome: 13.7 Discontinued due to adverse event.

Study or Subgroup	ABC/3TC/EFV Events	Total	TDF/FTC/EFV Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
13.7.1 Week 48						
Post 2010: ASSERT	25	192	20	193	100.0%	1.29 [0.69, 2.42]
Subtotal (95% CI)		**192**		**193**	**100.0%**	**1.29 [0.69, 2.42]**
Total events	25		20			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.81 (P = 0.42)



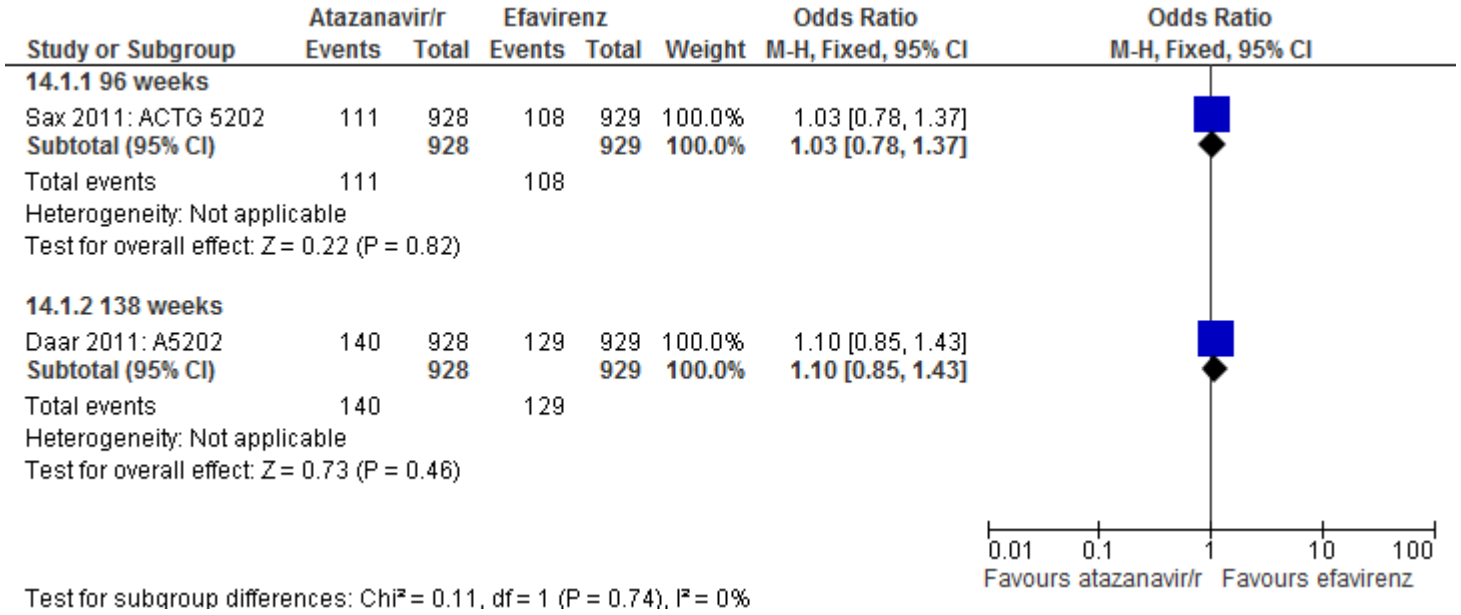
Test for subgroup differences: Not applicable

No data on other key outcomes.

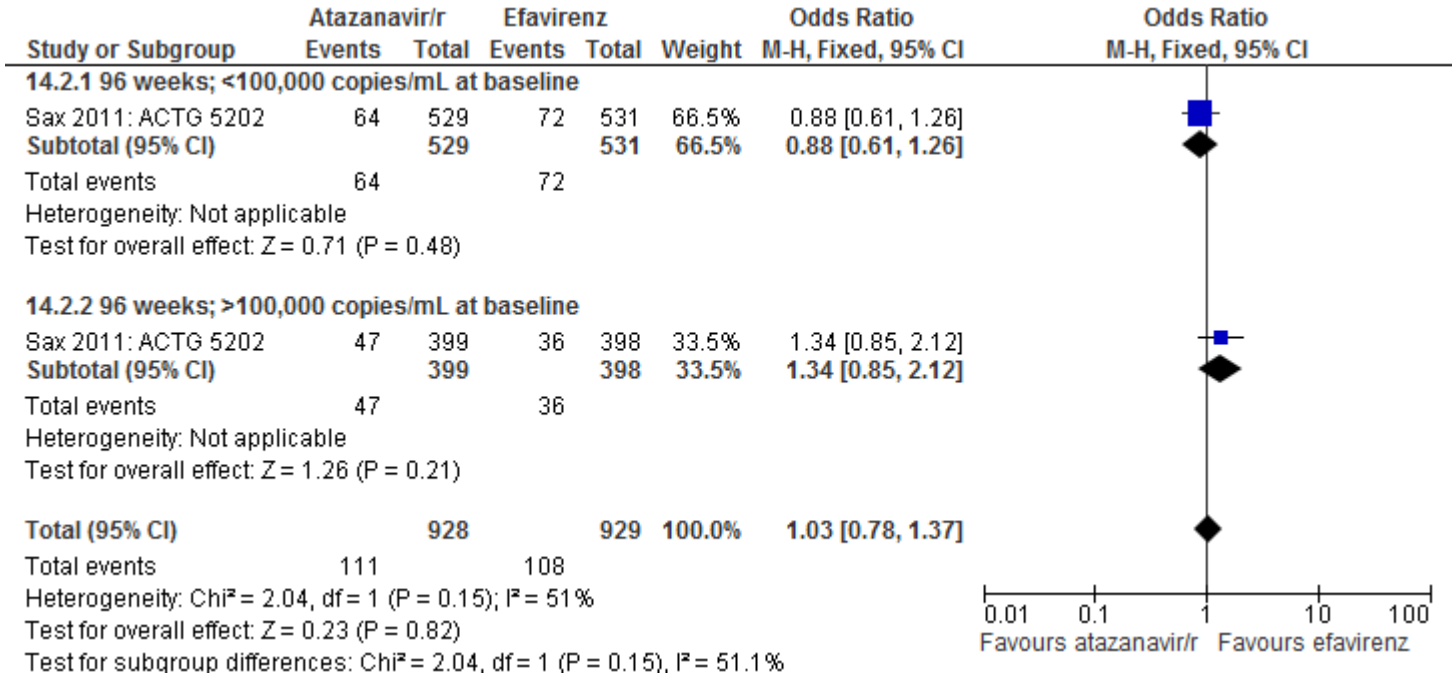
14 Atazanavir-ritonavir + ABC/3TC or TDF/FTC versus efavirenz + ABC/3TC or TDF/FTC

No new data since cut-off date of 17/9/2011 for key outcomes; study ACTG 5202 included in previous guidelines.

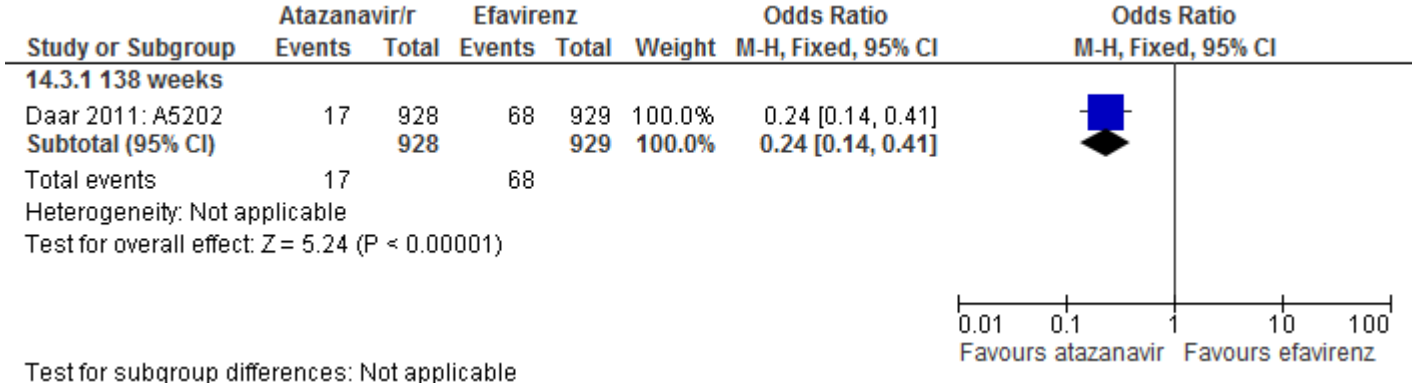
Forest plot of comparison: 14 Atazanavir-ritonavir + ABC/3TC or TDF/FTC versus efavirenz + ABC/3TC or TDF/FTC, outcome: 14.1 Virological failure.



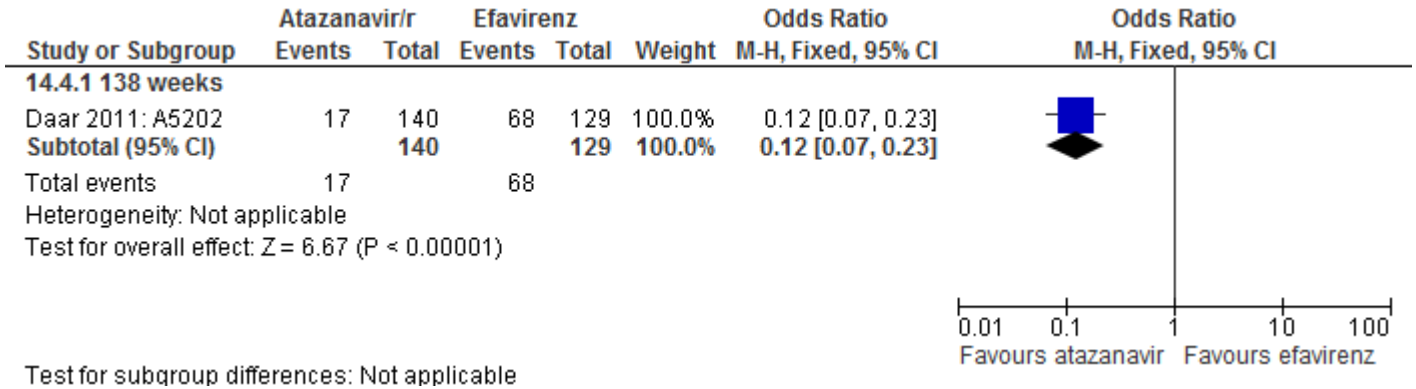
Forest plot of comparison: 14 Atazanavir-ritonavir + ABC/3TC or TDF/FTC versus efavirenz + ABC/3TC or TDF/FTC, outcome: 14.2 Virological failure; subgroups.



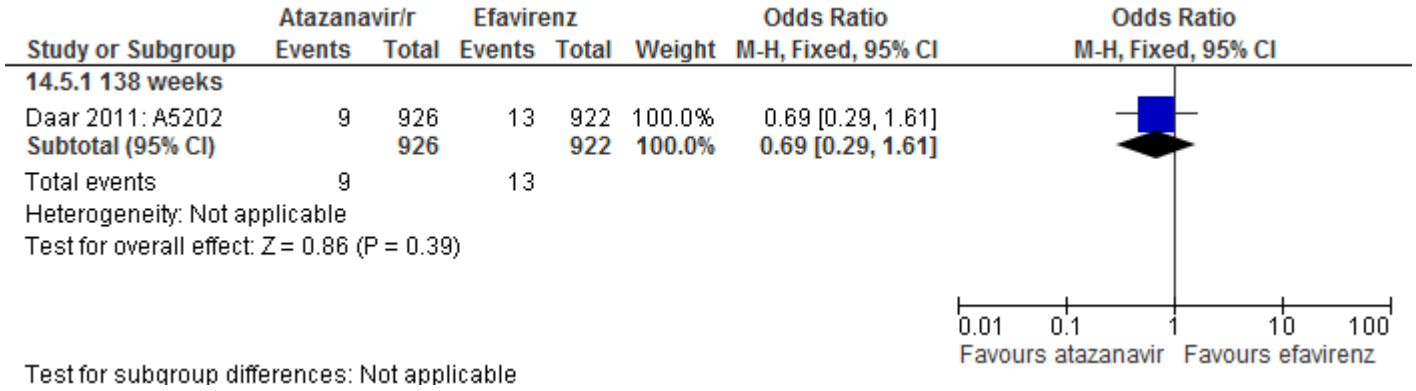
Forest plot of comparison: 14 Atazanavir-ritonavir + ABC/3TC or TDF/FTC versus efavirenz + ABC/3TC or TDF/FTC, outcome: 14.3 Resistance (% of total population).



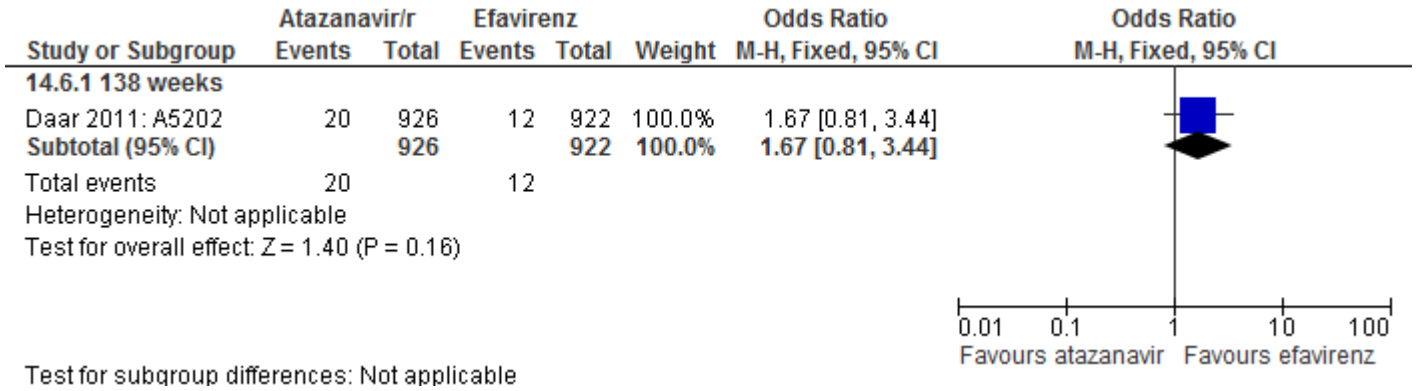
Forest plot of comparison: 14 Atazanavir-ritonavir + ABC/3TC or TDF/FTC versus efavirenz + ABC/3TC or TDF/FTC, outcome: 14.4 Resistance (% of patients with virological failure).



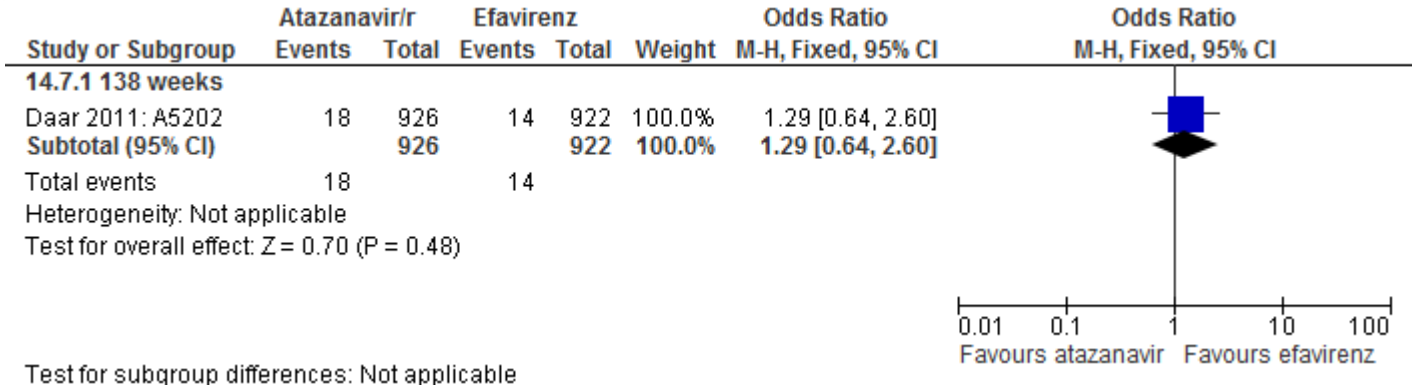
Forest plot of comparison: 14 Atazanavir-ritonavir + ABC/3TC or TDF/FTC versus efavirenz + ABC/3TC or TDF/FTC, outcome: 14.5 Grade 3 or 4 rash.



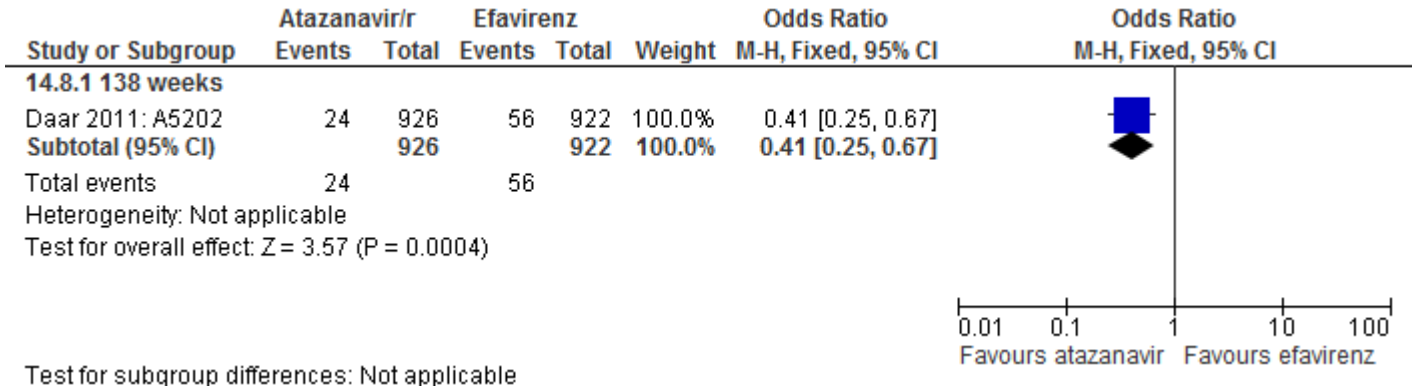
Forest plot of comparison: 14 Atazanavir-ritonavir + ABC/3TC or TDF/FTC versus efavirenz + ABC/3TC or TDF/FTC, outcome: 14.6 Grade 3 or 4 AST.



Forest plot of comparison: 14 Atazanavir-ritonavir + ABC/3TC or TDF/FTC versus efavirenz + ABC/3TC or TDF/FTC, outcome: 14.7 Grade 3 or 4 ALT.



Forest plot of comparison: 14 Atazanavir-ritonavir + ABC/3TC or TDF/FTC versus efavirenz + ABC/3TC or TDF/FTC, outcome: 14.8 Grade 3 or 4 CNS events.

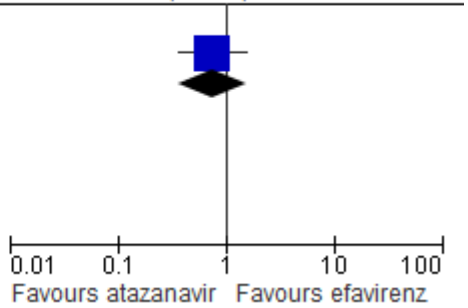


Forest plot of comparison: 14 Atazanavir-ritonavir + ABC/3TC or TDF/FTC versus efavirenz + ABC/3TC or TDF/FTC, outcome: 14.9 Grade 3 or 4 diarrhoea.

Study or Subgroup	Atazanavir/r Events	Total	Efavirenz Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
14.9.1 138 weeks						
Daar 2011: A5202	13	926	17	922	100.0%	0.76 [0.37, 1.57]
Subtotal (95% CI)		**926**		**922**	**100.0%**	**0.76 [0.37, 1.57]**
Total events	13		17			

Heterogeneity: Not applicable

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



Test for subgroup differences: Not applicable

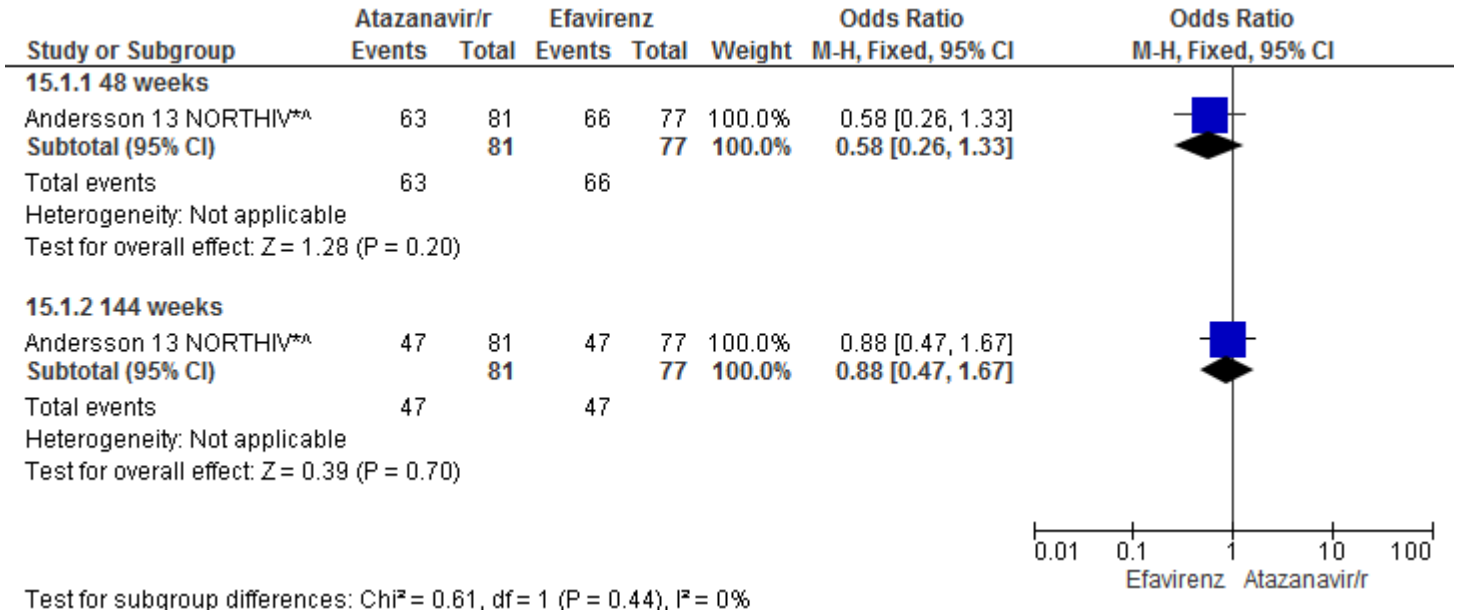
15 Atazanavir/r + 2 NRTI at physician's discretion versus efavirenz + 2 NRTI at physician's discretion

In the NORTHIV trial, patients were randomized to receive either efavirenz 600 mg once daily (EFV), or atazanavir 300 mg and ritonavir 100 mg once daily (AZV/r), or lopinavir 400 mg and ritonavir 100 mg twice daily (LPV/r), each given with 2 NRTIs. Treating physicians were allowed to choose the NRTIs at their own discretion and NRTI treatment could be changed during the study. No studies in the previous version of the guidelines with this comparison.

Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Length follow-up	Outcome measures	Funding
Lars-Magnus Andersson, Jan Vesterbacka, Anders Blaxhult, Leo Flamholc, Staffan Nilsson, Vidar Ormaasen, Anders Sönnerborg & Magnus Gisslén. Lopinavir/ritonavir, atazanavir/ritonavir, and efavirenz in antiretroviral-naïve HIV-1-infected individuals over 144 weeks: An open-label randomized controlled trial. Scandinavian Journal of Infectious Diseases 2013; 45: 543–551.	RCT NORTHIV Allocation to treatment Random Method of randomisation: block-randomisation (blocks of 6) with a concealed predefined computer-generated randomization list and was stratified by CD4 cell count (≤200 cells/µL or >200 cells/µL) and HIV-1 RNA level (≤100,000 copies/mL or >100,000 copies/mL) at enrolment. Concealment: concealed predefined computer-generated randomization	N=243 randomised; 239 of these received the allocated treatment and were analysed for efficacy. Thirty-nine of 81 (48%) patients who received the study treatment in the LPV/r group, 34 of 81 (42%) in the AZV/r group, and 30 of 77 (39%) in the EFV group discontinued treatment before week 144.	INCLUSION CRITERIA: Patients were recruited from centres at 29 sites in Norway and Sweden from April 2004 through December 2006, and were eligible for enrolment if they were infected with HIV-1, aged 16 y or older, naïve to ART, and fulfilled criteria in the Swedish national guidelines (2003) for initiation of treatment EXCLUSION CRITERIA: none stated. There were no restrictions in CD4 cell counts, and on-going opportunistic infection was not	AZV/r 300/100 mg once daily Given with 2 NRTIs. Treating physicians were allowed to choose the NRTIs at their own discretion and NRTI treatment could be changed during the study. Combinations of NRTIs used were: Abacavir + lamivudine; Tenofovir + emtricitabine; Zidovudine + lamivudine; or other 2 NRTI	EFV 600 mg once daily Third group: LPV/r 400/100 mg twice daily. Each given with 2 NRTIs. Treating physicians were allowed to choose the NRTIs at their own discretion and NRTI treatment could be changed during the study. Combinations of NRTIs used were: Abacavir + lamivudine; Tenofovir + emtricitabine; Zidovudine + lamivudine; or other 2 NRTI	Patients were assessed at screening, day 0 (baseline), and at weeks 1, 2, 3, 4, 12, 24, 48, 72, 96, 120, and 144.	Vital signs and samples for plasma HIV-1 RNA, CD4 cell count, and laboratory tests (serum chemistry and haematology, and fasting lipid profile). Confirmed virological response, non-completer equals failure (CVR, NCF), time to loss of virological response (TLOVR), US Food and Drug Administration (FDA) snapshot analysis, and virological response-on treatment (VR-OT). Median changes in CD4 cell counts from baseline through week 144 were compared	This study was supported by grants from the Swedish Research Council (K2008-58P-20930-04-1, project 2007-7092), the Sahlgrenska Academy at University of Gothenburg (ALFGBG-11067), Goteborg Medical Society, the Research Foundation Swedish Physicians against AIDS, and Vastra Gotalandsregionens FoU-anslag (VGFOUREG-25921)

	list Blinding: open-label Sample size calculation: The enrolment sample sizes were sufficient to achieve a 2-sided comparison of proportions between 2 samples with the possibility of detecting a difference in proportions as small as h = 0.3 (Cohen's h) with 80% power at the 5% significance level. ITT analysis: Yes Setting: Outpatients		an exclusion criterion. Baseline comparability between groups: yes Age: Lopinavir/r: 37 (32 – 45); Atazanavir/r: 39 (34 – 51); Efavirenz: 37 (31 – 46) Gender: female: 36 (29%); 31 (25%); 36 (28%) Severity of disease: median CD4 cell count: 150 (90 – 216); 170 (80 – 220); 150 (80 – 200)				between treatment regimens based on observed values (and last observation carried forward). Analyses of fasting lipids over time excluded values obtained after initiation of serum lipid reduction therapy. Median percent changes in fasting lipids from baseline were compared between treatment regimens on observed cases (and LOCF).	

Forest plot of comparison: 15 Atazanavir/r + 2 NRTI versus efavirenz + 2 NRTI, outcome: 15.1 HIV-1 RNA below 50 copies/ml.



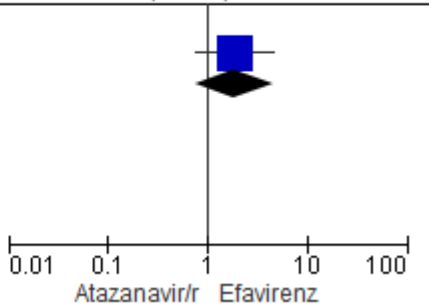
Subgroup analysis by < or > 100,000 copies/mL at baseline not shown.

Forest plot of comparison: 15 Atazanavir/r + 2 NRTI versus efavirenz + 2 NRTI, outcome: 15.2 Virological failure.

Study or Subgroup	Atazanavir/r Events	Total	Efavirenz Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
15.2.1 144 weeks						
Andersson 13 NORTHIV*^	16	81	9	77	100.0%	1.86 [0.77, 4.50]
Subtotal (95% CI)		**81**		**77**	**100.0%**	**1.86 [0.77, 4.50]**
Total events	16		9			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.37 (P = 0.17)



Test for subgroup differences: Not applicable

Subgroup analysis by < or > 100,000 copies/mL at baseline not shown.

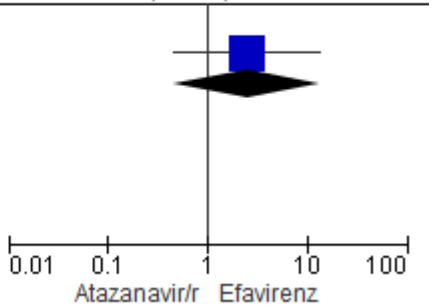
No data on resistance.

Forest plot of comparison: 15 Atazanavir/r + 2 NRTI versus efavirenz + 2 NRTI, outcome: 15.3 Discontinued due to serious adverse events.

Study or Subgroup	Atazanavir/r Events	Total	Efavirenz Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
15.3.1 144 weeks						
Andersson 13 NORTHIV*^	5	81	2	77	100.0%	2.47 [0.46, 13.11]
Subtotal (95% CI)		**81**		**77**	**100.0%**	**2.47 [0.46, 13.11]**
Total events	5		2			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.06 (P = 0.29)



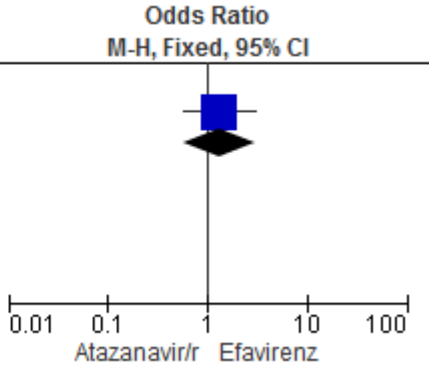
Test for subgroup differences: Not applicable

Forest plot of comparison: 15 Atazanavir/r + 2 NRTI versus efavirenz + 2 NRTI, outcome: 15.4 Serious adverse events (unclear if clinical or laboratory).

Study or Subgroup	Atazanavir/r Events	Total	Efavirenz Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
15.4.1 144 weeks						
Andersson 13 NORTHIV*^	16	81	12	77	100.0%	1.33 [0.59, 3.04]
Subtotal (95% CI)		**81**		**77**	**100.0%**	**1.33 [0.59, 3.04]**
Total events	16		12			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.68 (P = 0.49)



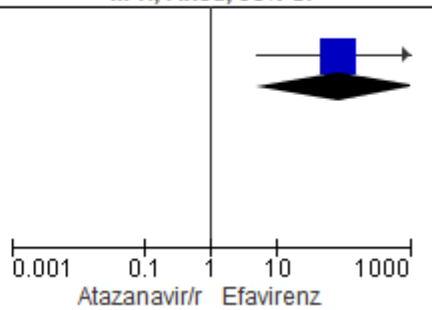
Test for subgroup differences: Not applicable

Forest plot of comparison: 15 Atazanavir/r + 2 NRTI versus efavirenz + 2 NRTI, outcome: 15.5 Grade 3-4 total bilirubin elevation (≥2.6 x ULN).

Study or Subgroup	Atazanavir/r Events	Total	Efavirenz Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
15.5.1 144 weeks						
Andersson 13 NORTHIV*^	27	74	0	72	100.0%	83.95 [5.00, 1409.39]
Subtotal (95% CI)		**74**		**72**	**100.0%**	**83.95 [5.00, 1409.39]**
Total events	27		0			

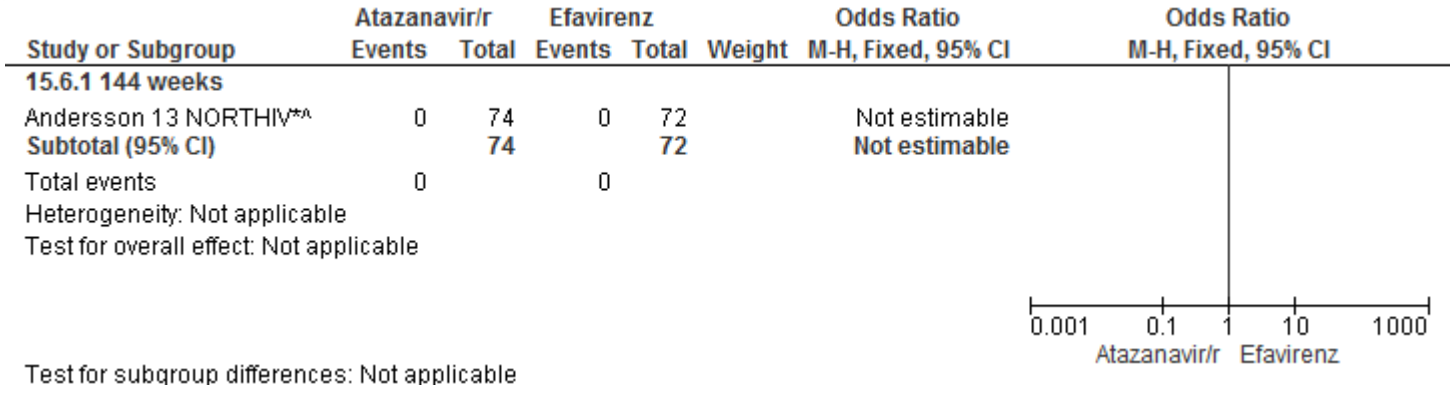
Heterogeneity: Not applicable

Test for overall effect: Z = 3.08 (P = 0.002)

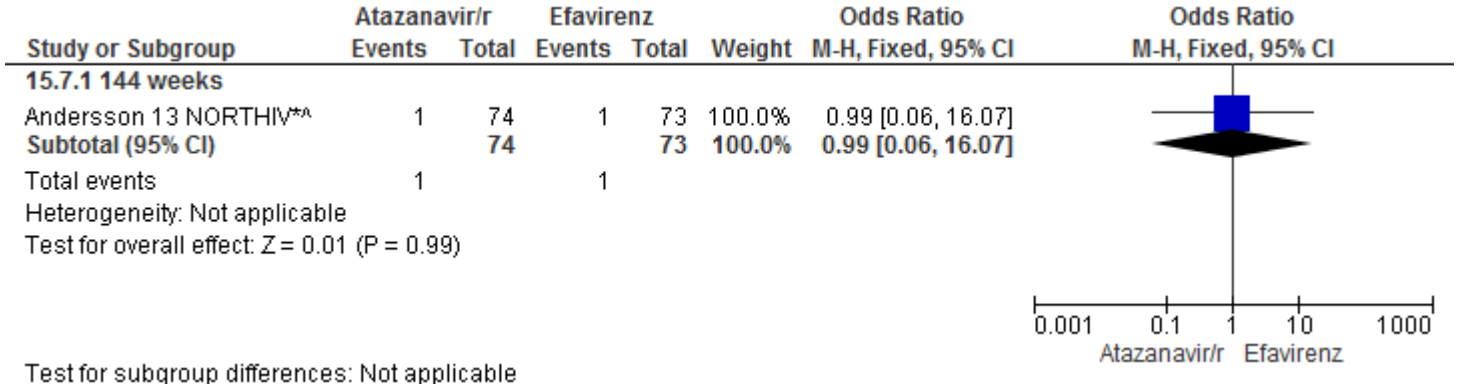


Test for subgroup differences: Not applicable

Forest plot of comparison: 15 Atazanavir/r + 2 NRTI versus efavirenz + 2 NRTI, outcome: 15.6 Grade 3-4 triglyceride (≥8.51 mmol/L).



Forest plot of comparison: 15 Atazanavir/r + 2 NRTI versus efavirenz + 2 NRTI, outcome: 15.7 Grade 3-4 ALT elevation (≥5.1 x ULN).



No data on Grade 3-4 rash, CNS events of diarrhoea.

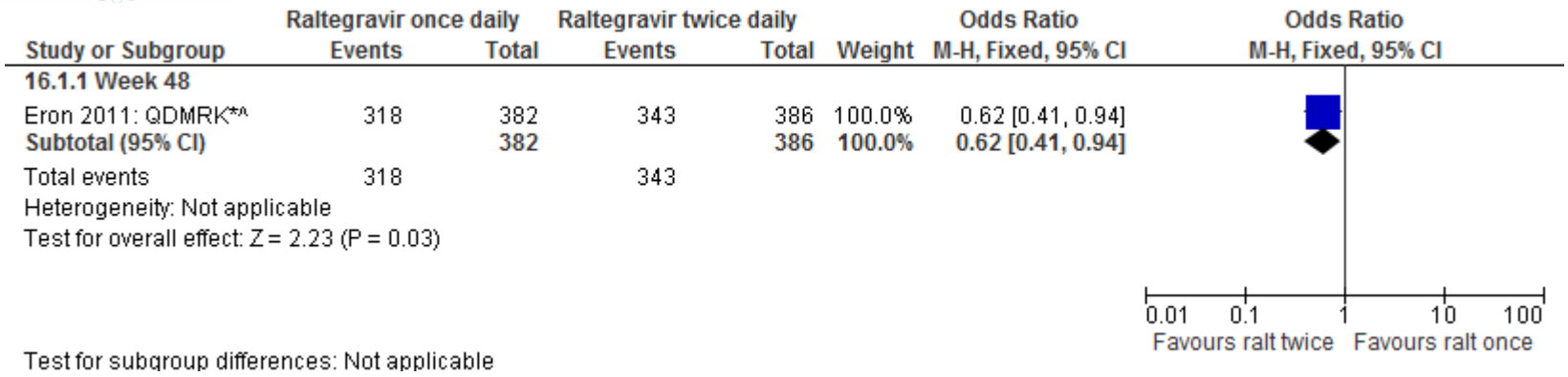
16 Raltegravir once daily + tenofovir-emtricitabine versus raltegravir twice daily + tenofovir-emtricitabine

Eron 2011 (QDMRK study) was published on 19 September 2011, was cited in the previous guidelines, but evidence table/data not shown.

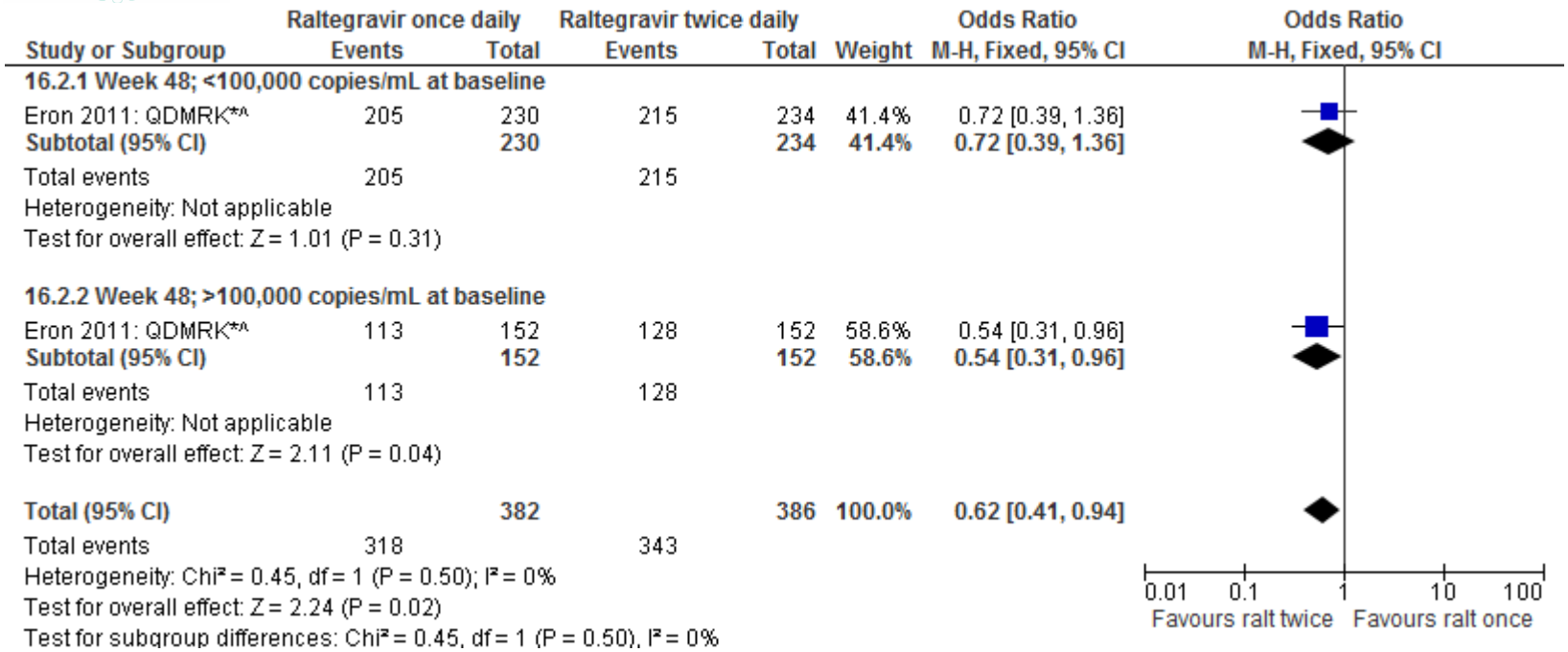
Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Length follow-up	Outcome measures	Funding
Joseph J Eron Jr et al for the QDMRK Investigators. Raltegravir once daily or twice daily in previously untreated patients with HIV-1: a randomised, active-controlled, phase 3 non-inferiority trial. Lancet Infect Dis 2011; 11: 907–15	Design: double-blind, randomised, phase 3 non-inferiority study (NCT00745823; QDMRK; MK-0518 protocol 071) Randomisation: Computer - generated randomised allocation schedule. Patients were stratified by screening viral RNA loads (>100 000 copies per mL vs ≤100 000 copies per mL) and viral hepatitis co-infection status. Allocation concealment: central interactive voice response system Blinding: Investigators, study site personnel, patients, monitors, and central laboratory personnel were masked to treatment allocation. Comparable groups at baseline: Baseline characteristics were balanced between treatment groups Sample size calculation: With 375 patients in both treatment groups, assuming a true response rate of	775	Inclusion: previously untreated adults (≥18 years) with plasma HIV RNA viral loads of more than 5000 copies per mL. Patients with stable compensated chronic hepatitis could be enrolled. Exclusion: patients who had acute or decompensated chronic hepatitis, renal insufficiency (defined as dependency on dialysis, serum creatinine concentration of more than twice the upper limit of the normal, or an estimated creatinine clearance of 30 mL per min or less calculated with the Cockcroft-Gault formula), or any medical disorder likely to interfere with the undertaking or interpretation of the study. Women who were pregnant or breastfeeding were ineligible. Patients infected with HIV that was resistant to tenofovir or emtricitabine were excluded.	Raltegravir once daily (two 400 mg tablets taken together about 24 h apart) with corresponding matching-image placebos, n=386. All participants also received tenofovir 300 mg and emtricitabine 200 mg coformulated as one tablet (Truvada) to be taken according to local practice.	Raltegravir twice daily (one 400 mg tablet about 12 h apart) with corresponding matching-image placebos, n=389. All participants also received tenofovir 300 mg and emtricitabine 200 mg coformulated as one tablet (Truvada) to be taken according to local practice.	48 weeks	For the primary efficacy analysis, the authors postulated that once-daily raltegravir would have non-inferior anti-retroviral activity compared with twice-daily raltegravir in terms of the proportion of patients in both groups achieving virological response at 48 weeks. Once-daily raltegravir was to be regarded as non-inferior to twice-daily raltegravir if the lower bound of the two-sided	Merck

	80% at week 48 for both treatment groups and with a non-completers equals failures approach, the study would have about 90% power to show non-inferiority of once-daily raltegravir to twice-daily raltegravir after adjustment for a small loss in power as a result of the two planned interim futility analyses before the main efficacy analysis at 48 weeks. Intention to treat analysis: For calculation of virological response rates, the authors used a modified intention-to-treat analysis that included all randomised patients receiving at least one dose of study medication, and counting all non-completers as failures. Drop out: 14/775 (2%) lost to follow up Setting: 83 centres (mostly outpatient offices or clinics) on six continents						95% CI for the difference in response rate (once-daily raltegravir minus twice-daily raltegravir) was above –10%. Secondary efficacy outcomes included the proportion of patients achieving plasma viral loads of fewer than 400 copies per mL and change in CD4 cell counts from baseline in each treatment group.	

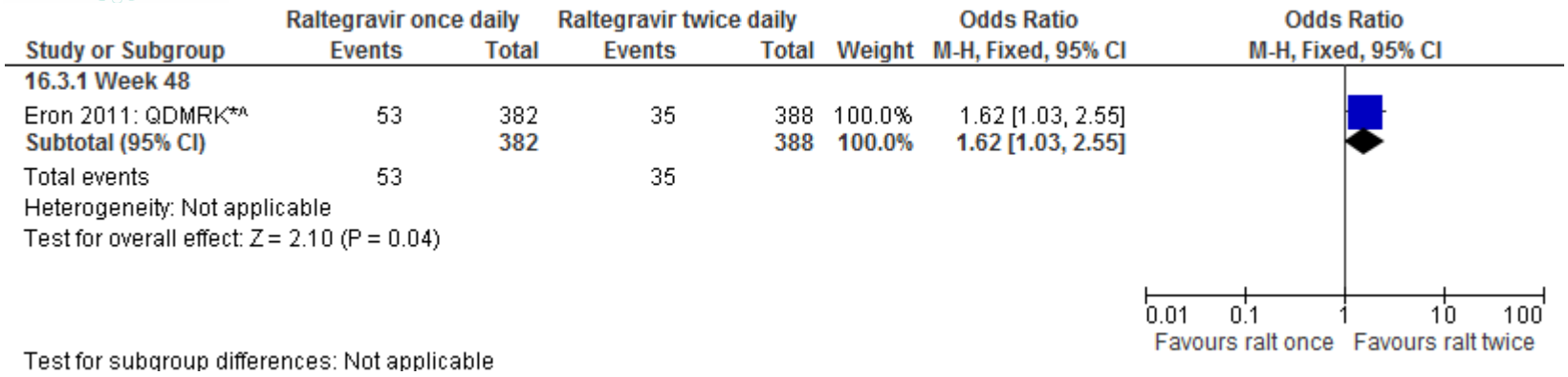
Forest plot of comparison: 16 Raltegravir once daily + tenofovir-emtricitabine versus raltegravir twice daily + tenofovir-emtricitabine, outcome: 16.1 Virological response.



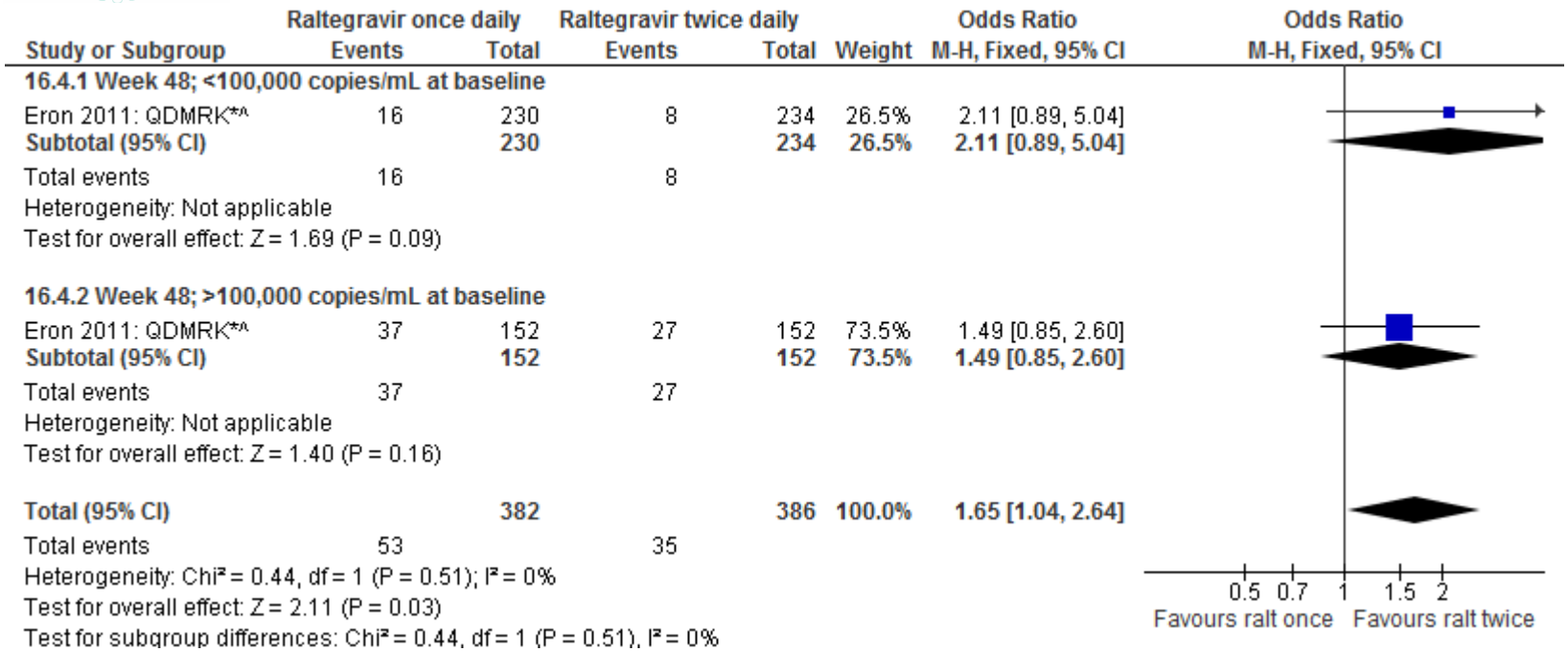
Forest plot of comparison: 16 Raltegravir once daily + tenofovir-emtricitabine versus raltegravir twice daily + tenofovir-emtricitabine, outcome: 16.2 Virological response; subgroups.



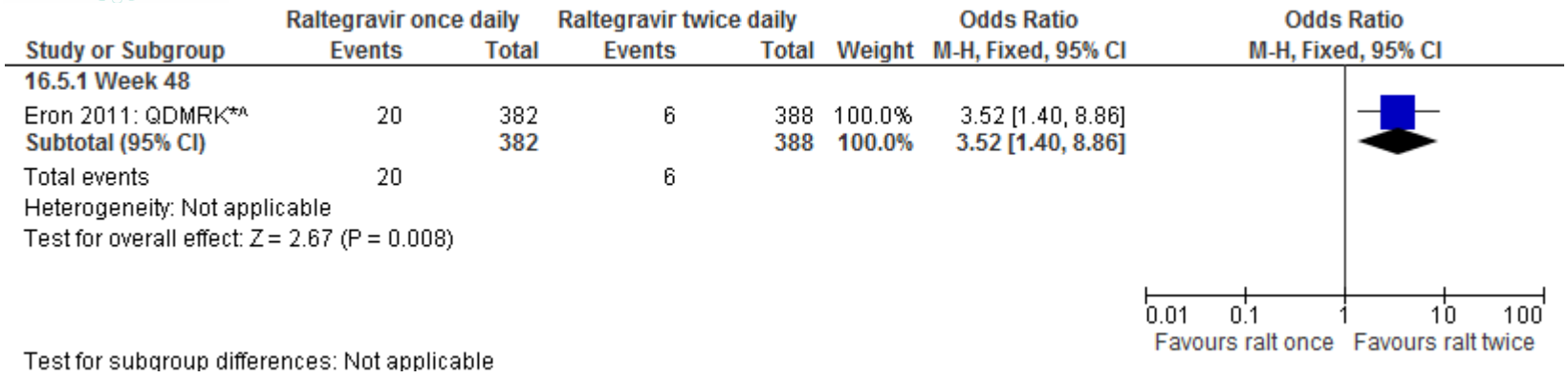
Forest plot of comparison: 16 Raltegravir once daily + tenofovir-emtricitabine versus raltegravir twice daily + tenofovir-emtricitabine, outcome: 16.3 Virological failure.



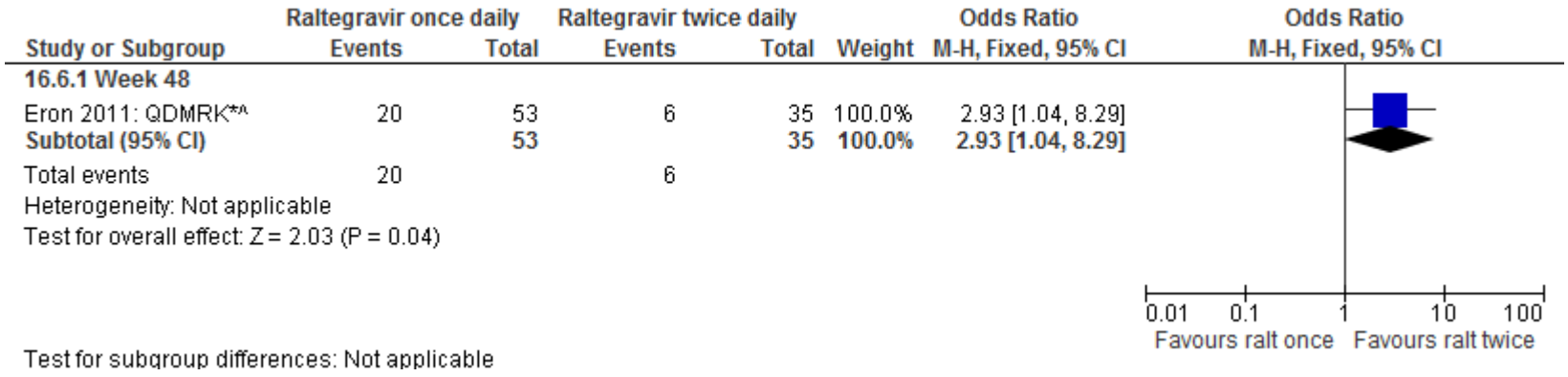
Forest plot of comparison: 16 Raltegravir once daily + tenofovir-emtricitabine versus raltegravir twice daily + tenofovir-emtricitabine, outcome: 16.4 Virological failure; subgroups.



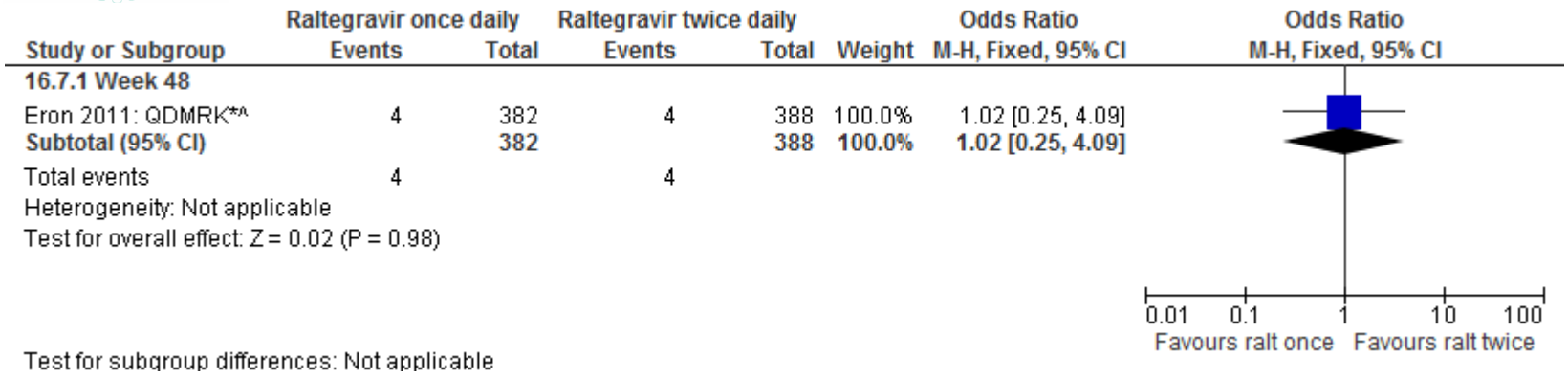
Forest plot of comparison: 16 Raltegravir once daily + tenofovir-emtricitabine versus raltegravir twice daily + tenofovir-emtricitabine, outcome: 16.5 Resistance (% total population).



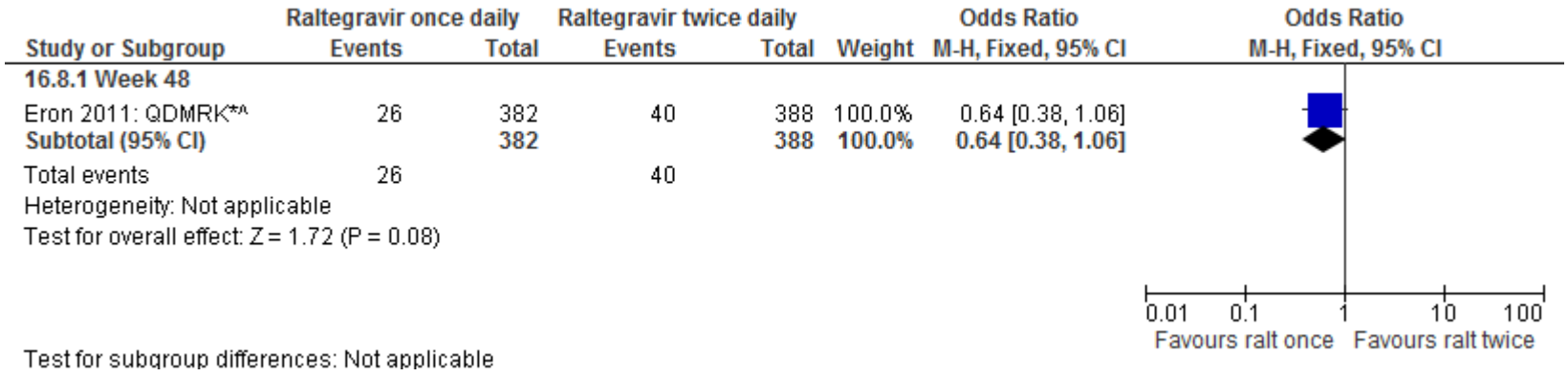
Forest plot of comparison: 16 Raltegravir once daily + tenofovir-emtricitabine versus raltegravir twice daily + tenofovir-emtricitabine, outcome: 16.6 Resistance (% patients with virological failure).



Forest plot of comparison: 16 Raltegravir once daily + tenofovir-emtricitabine versus raltegravir twice daily + tenofovir-emtricitabine, outcome: 16.7 Discontinued due to adverse event.



Forest plot of comparison: 16 Raltegravir once daily + tenofovir-emtricitabine versus raltegravir twice daily + tenofovir-emtricitabine, outcome: 16.8 Serious adverse event.



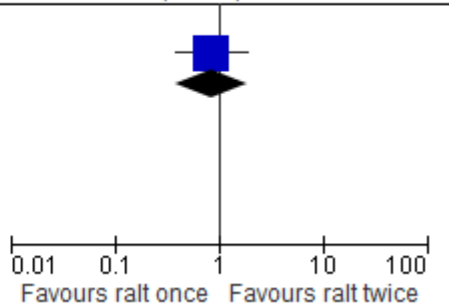
Forest plot of comparison: 16 Raltegravir once daily + tenofovir-emtricitabine versus raltegravir twice daily + tenofovir-emtricitabine, outcome: 16.9 Grade 3 or 4 raised alanine aminotransferase.

Study or Subgroup	Raltegravir once daily Events	Total	Raltegravir twice daily Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
16.9.1 Week 48						
Eron 2011: QDMRK*^	11	380	13	386	100.0%	0.86 [0.38, 1.93]
Subtotal (95% CI)		**380**		**386**	**100.0%**	**0.86 [0.38, 1.93]**
Total events	11		13			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.38 (P = 0.71)

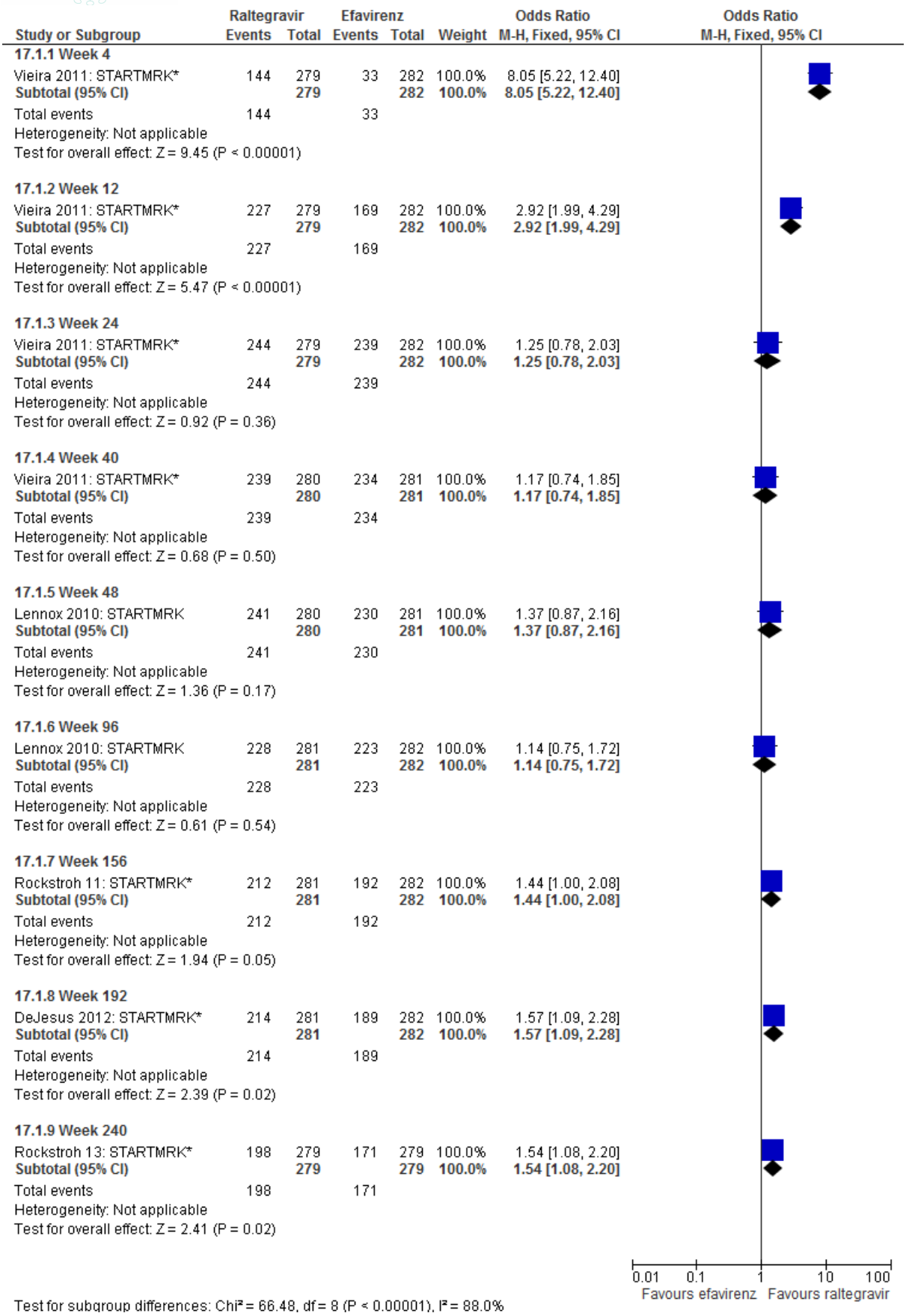
Test for subgroup differences: Not applicable



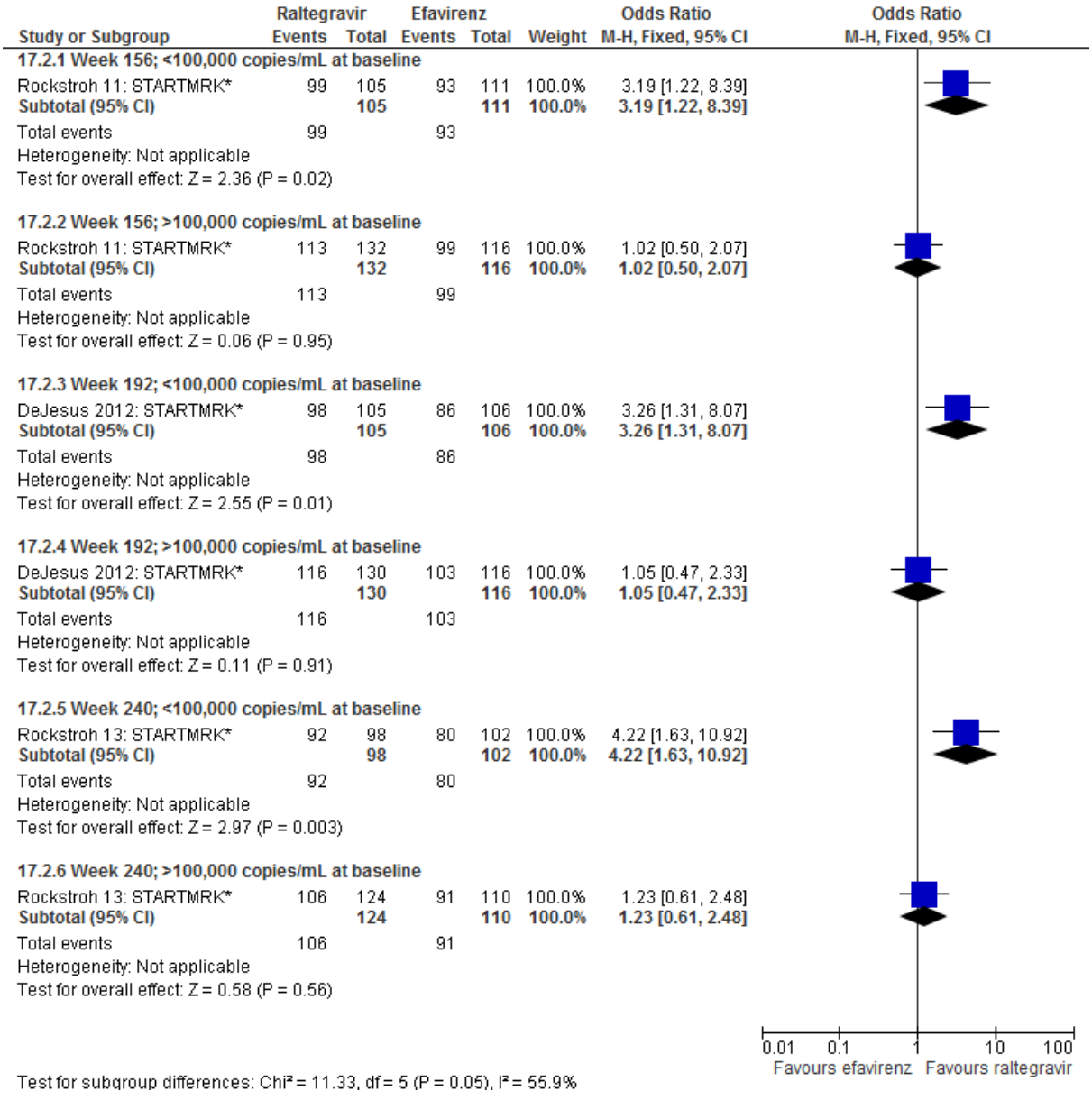
17 Raltegravir + tenofovir/ emtricitabine versus efavirenz + tenofovir/ emtricitabine

No new studies; later papers from STARTMRK study (study characteristics in previous guideline).

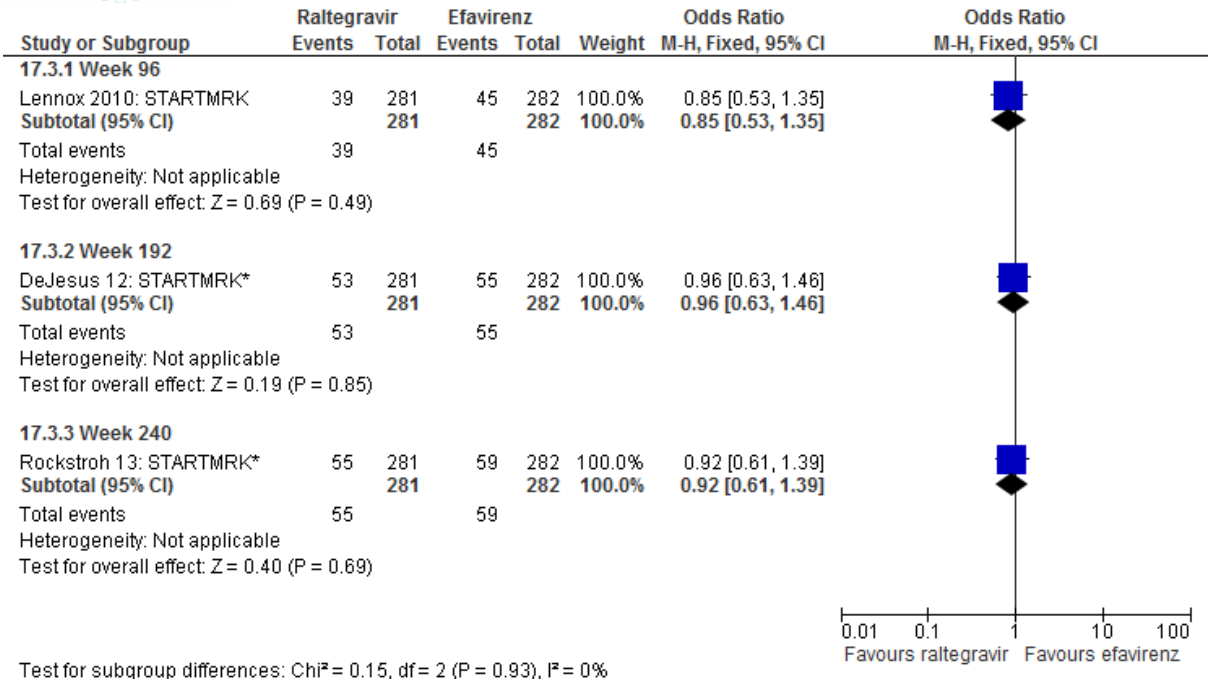
Forest plot of comparison: 17 Raltegravir + tenofovir/ emtricitabine versus efavirenz + tenofovir/ emtricitabine, outcome: 17.1 vRNA levels <50 copies/mL.


Raltegravir
Efavirenz
Odds Ratio
Odds Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
17.1.1 Week 4
Vieira 2011: STARTMRK* 144 279 33 282 100.0% 8.05 [5.22, 12.40]
Subtotal (95% CI) 279 282 100.0% 8.05 [5.22, 12.40]
Total events 144 33
Heterogeneity: Not applicable
Test for overall effect: Z = 9.45 (P < 0.00001)
17.1.2 Week 12
Vieira 2011: STARTMRK* 227 279 169 282 100.0% 2.92 [1.99, 4.29]
Subtotal (95% CI) 279 282 100.0% 2.92 [1.99, 4.29]
Total events 227 169
Heterogeneity: Not applicable
Test for overall effect: Z = 5.47 (P < 0.00001)
17.1.3 Week 24
Vieira 2011: STARTMRK* 244 279 239 282 100.0% 1.25 [0.78, 2.03]
Subtotal (95% CI) 279 282 100.0% 1.25 [0.78, 2.03]
Total events 244 239
Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)
17.1.4 Week 40
Vieira 2011: STARTMRK* 239 280 234 281 100.0% 1.17 [0.74, 1.85]
Subtotal (95% CI) 280 281 100.0% 1.17 [0.74, 1.85]
Total events 239 234
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
17.1.5 Week 48
Lennox 2010: STARTMRK 241 280 230 281 100.0% 1.37 [0.87, 2.16]
Subtotal (95% CI) 280 281 100.0% 1.37 [0.87, 2.16]
Total events 241 230
Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.17)
17.1.6 Week 96
Lennox 2010: STARTMRK 228 281 223 282 100.0% 1.14 [0.75, 1.72]
Subtotal (95% CI) 281 282 100.0% 1.14 [0.75, 1.72]
Total events 228 223
Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)
17.1.7 Week 156
Rockstroh 11: STARTMRK* 212 281 192 282 100.0% 1.44 [1.00, 2.08]
Subtotal (95% CI) 281 282 100.0% 1.44 [1.00, 2.08]
Total events 212 192
Heterogeneity: Not applicable
Test for overall effect: Z = 1.94 (P = 0.05)
17.1.8 Week 192
DeJesus 2012: STARTMRK* 214 281 189 282 100.0% 1.57 [1.09, 2.28]
Subtotal (95% CI) 281 282 100.0% 1.57 [1.09, 2.28]
Total events 214 189
Heterogeneity: Not applicable
Test for overall effect: Z = 2.39 (P = 0.02)
17.1.9 Week 240
Rockstroh 13: STARTMRK* 198 279 171 279 100.0% 1.54 [1.08, 2.20]
Subtotal (95% CI) 279 279 100.0% 1.54 [1.08, 2.20]
Total events 198 171
Heterogeneity: Not applicable
Test for overall effect: Z = 2.41 (P = 0.02)
0.01 0.1 1 10 100
Favours efavirenz Favours raltegravir
Test for subgroup differences: Chi² = 66.48, df = 8 (P < 0.00001), I² = 88.0%

Forest plot of comparison: 17 Raltegravir + tenofovir/ emtricitabine versus efavirenz + tenofovir/ emtricitabine, outcome: 17.2 vRNA levels <50 copies/mL; subgroups.

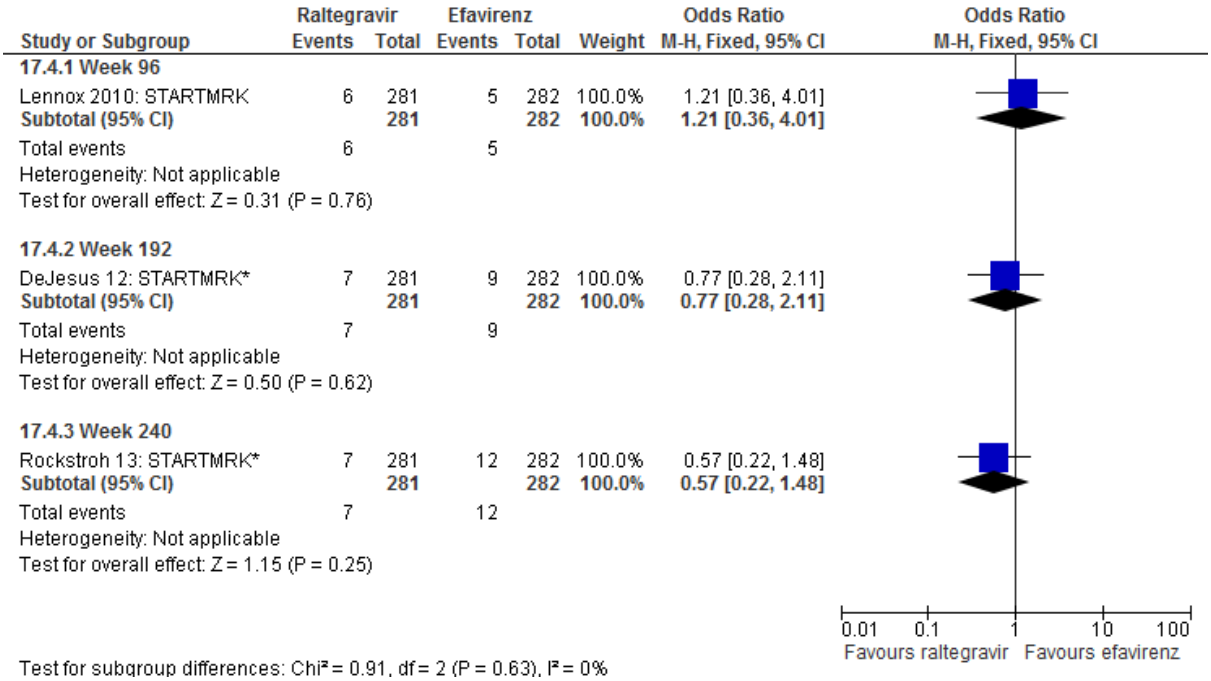


Forest plot of comparison: 17 Raltegravir + tenofovir/ emtricitabine versus efavirenz + tenofovir/ emtricitabine, outcome: 17.3 Virological failure.

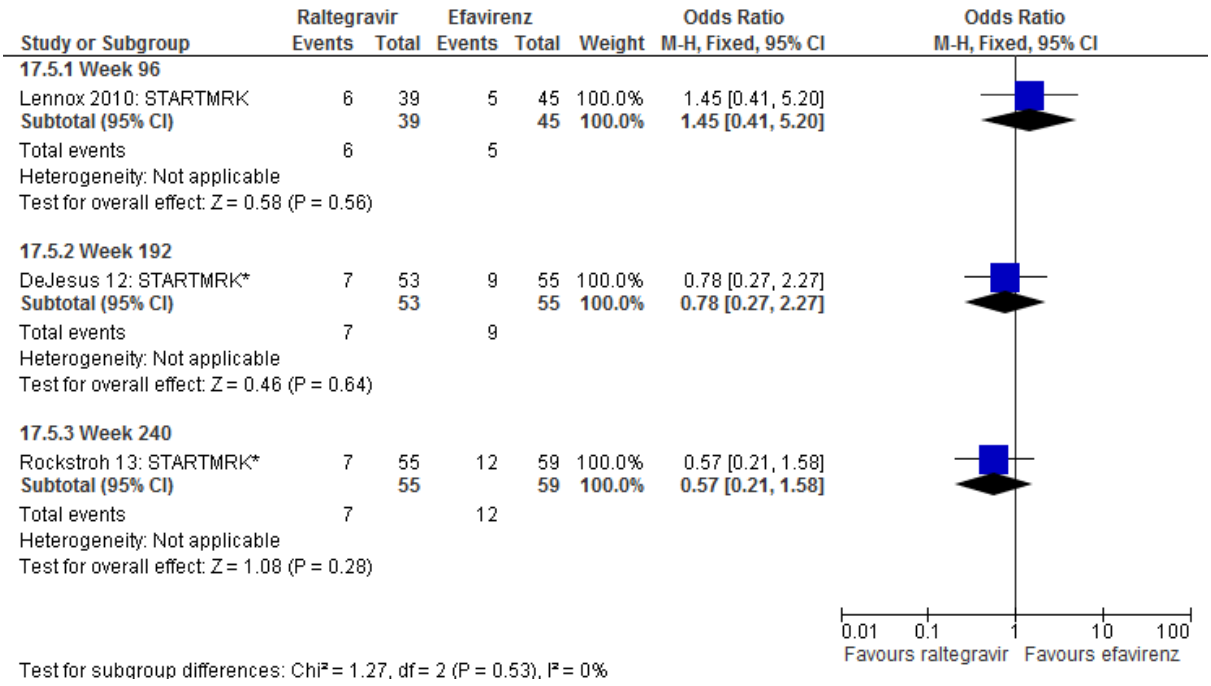


Subgroups by < or > 100,000 copies/mL not available.

Forest plot of comparison: 17 Raltegravir + tenofovir/ emtricitabine versus efavirenz + tenofovir/ emtricitabine, outcome: 17.4 Resistance (% total population).



Forest plot of comparison: 17 Raltegravir + tenofovir/ emtricitabine versus efavirenz + tenofovir/ emtricitabine, outcome: 17.5 Resistance (% of those with virological failure).

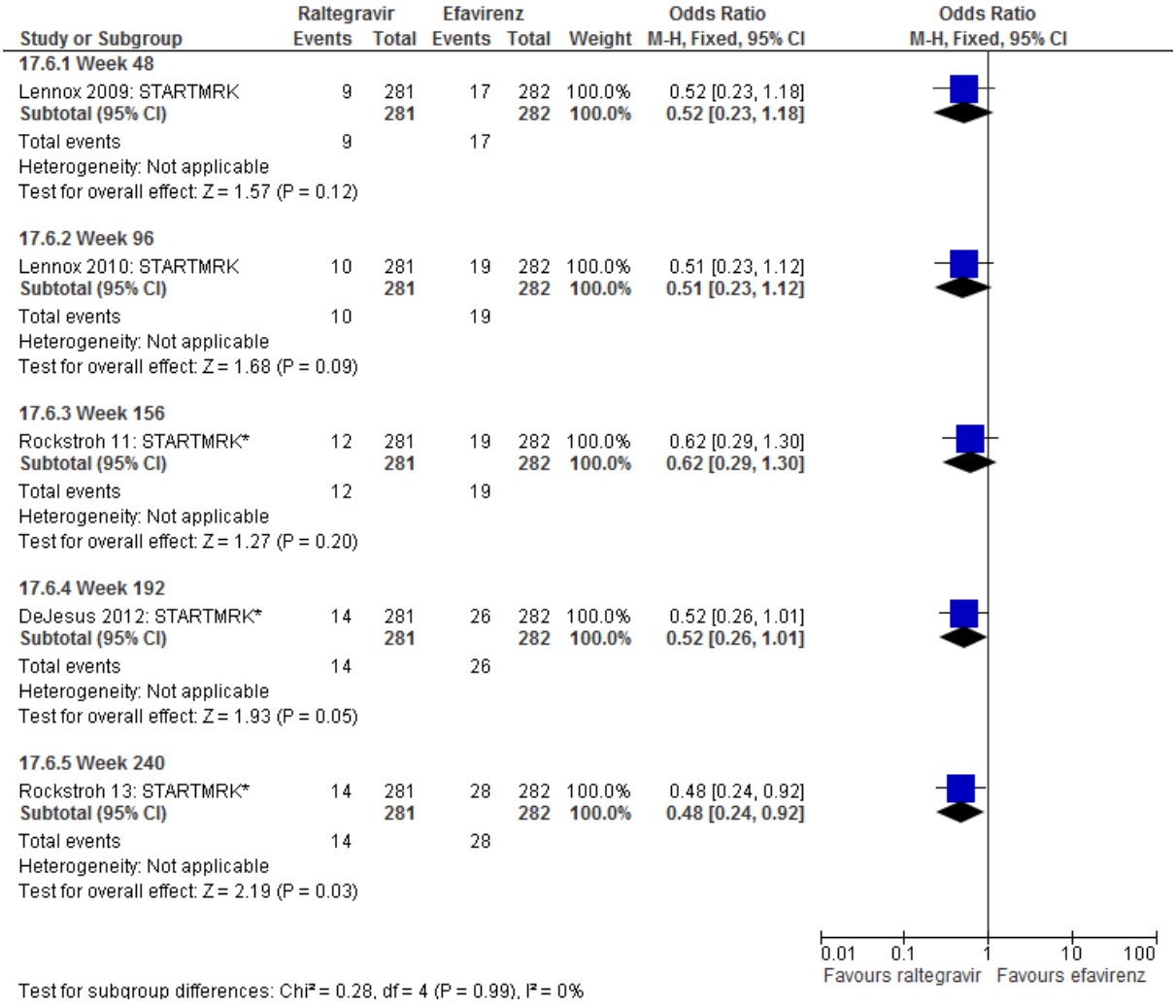


Cumulatively through week 192, 108 patients experienced virologic failure, including 21/53 raltegravir recipients and 17/55 efavirenz recipients with vRNA levels >400 copies/mL (potentially allowing genotypic resistance testing). Raltegravir-resistant virus was demonstrated in 4 of the 21 evaluable patients in the raltegravir group (1 case each showing Q148H+G140S, Q148R+G140S, Y143H+L74L/M+E92Q+T97A, and Y143R); in 3 of these 4 cases, the viruses had dual raltegravir- and emtricitabine-resistance but remained sensitive to tenofovir. Emtricitabine resistance was detected in 3 additional cases (including in 1 patient with raltegravir-susceptible virus and in 2 other patients where the integrase gene was not amplified). Efavirenz-resistant virus was demonstrated in 7 of the 17 evaluable patients in the efavirenz group (all had the K103N substitution, with K103N as the sole mutation in 3 instances); the viruses were also emtricitabine-resistant but susceptible to tenofovir in 3 of these 7 cases and resistant to both emtricitabine and tenofovir in 1 case. In 2 additional efavirenz recipients, only emtricitabine resistance was detected.

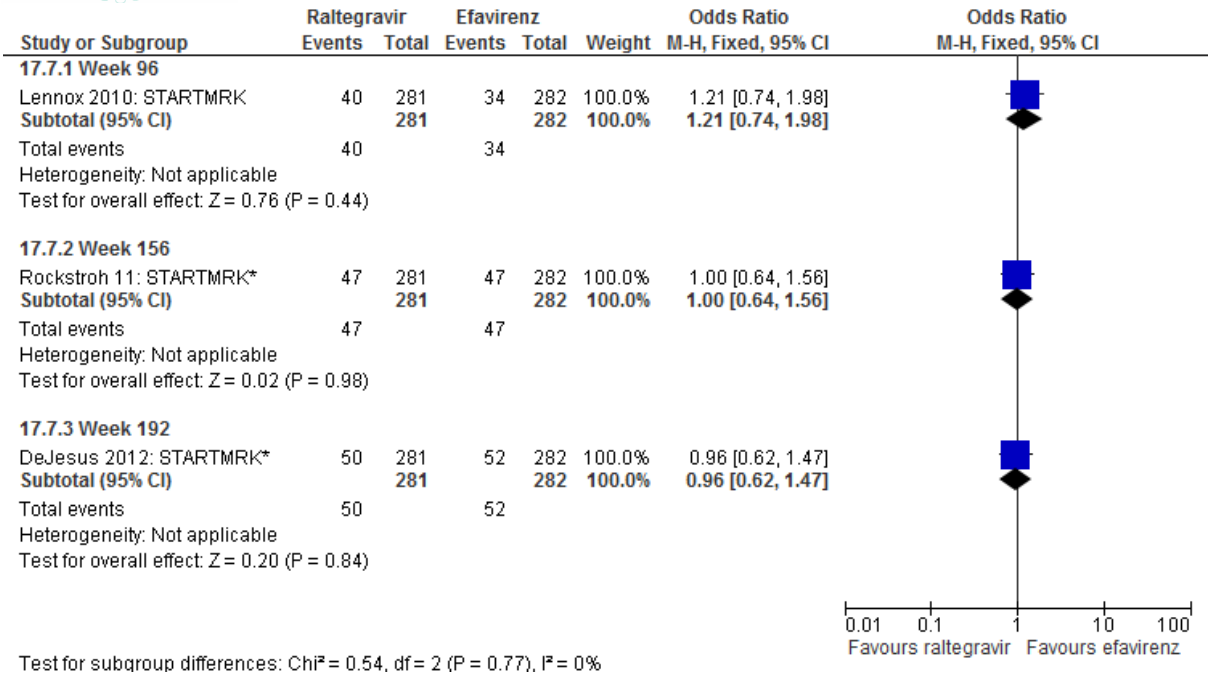
Cumulatively through week 240, 114 patients experienced virologic failure, including 23 of 55 raltegravir recipients and 20 of 59 efavirenz recipients with vRNA levels >400 copies per milliliter, allowing virus amplification for resistance testing. Raltegravir-resistant virus was demonstrated in 4 of the 23 patients in the raltegravir group with sequencing data (1 case each showing Q148H + G140S, Q148R + G140S, Y143Y/H + L74L/M + E92Q +T97A, and Y143R); in 3 of these 4 cases, the viruses had dual raltegravir- and emtricitabine-resistance but remained sensitive to tenofovir. Emtricitabine resistance was detected in 3 additional cases (including in 1 patient with raltegravir susceptible virus and in 2 other patients where the integrase gene was not amplified). Efavirenz-resistant virus was demonstrated in 10 of the 17 patients in the efavirenz group with sequencing data (all had the K103N substitution, with K103N as the sole mutation in 3 instances); the viruses were also emtricitabine resistant but susceptible to tenofovir in 3 of these 10 cases and resistant to

both emtricitabine and tenofovir in 1 case. In 2 additional efavirenz recipients, only emtricitabine resistance was detected.

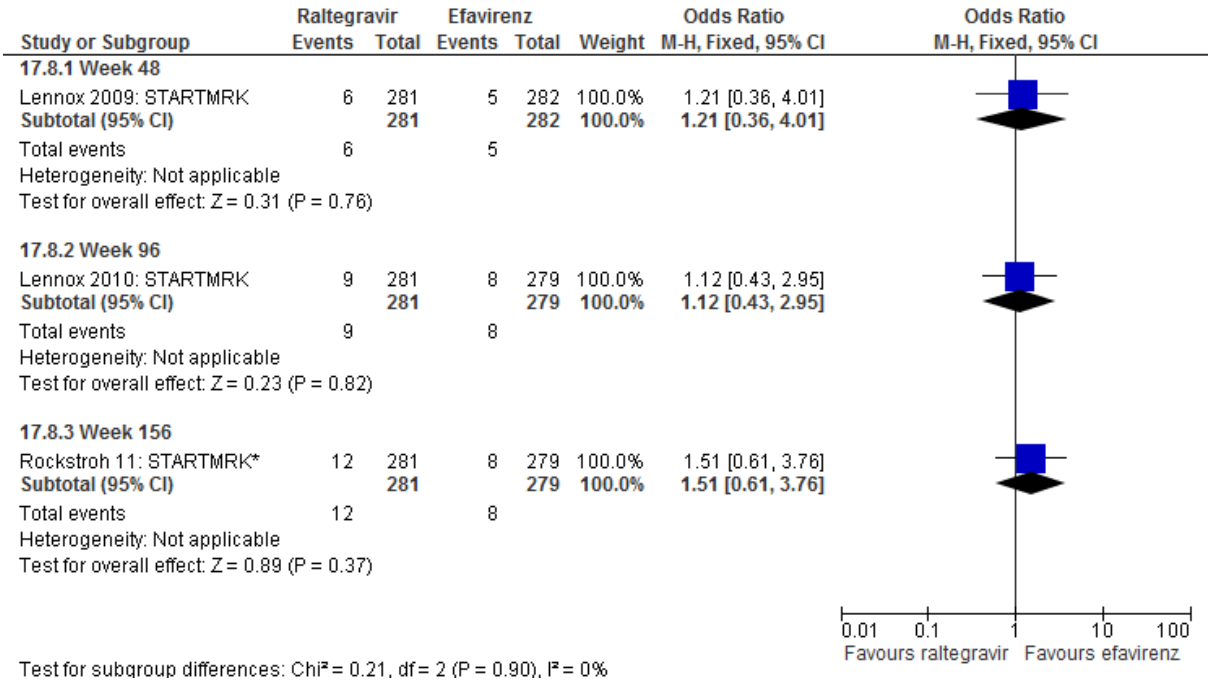
Forest plot of comparison: 17 Raltegravir + tenofovir/ emtricitabine versus efavirenz + tenofovir/ emtricitabine, outcome: 17.6 Discontinued study (adverse events).



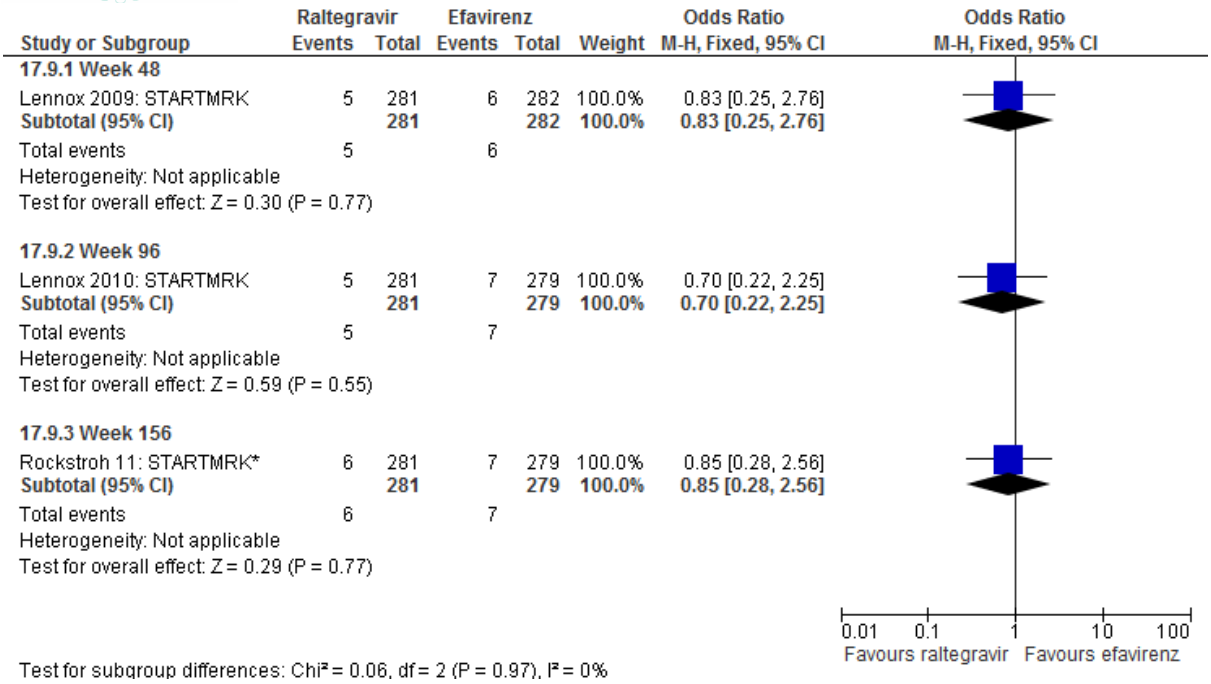
Forest plot of comparison: 17 Raltegravir + tenofovir/ emtricitabine versus efavirenz + tenofovir/ emtricitabine, outcome: 17.7 1 or more serious clinical adverse events.



Forest plot of comparison: 17 Raltegravir + tenofovir/ emtricitabine versus efavirenz + tenofovir/ emtricitabine, outcome: 17.8 Treatment-emergent grade 3/4 abnormality in aspartate aminotransferase.



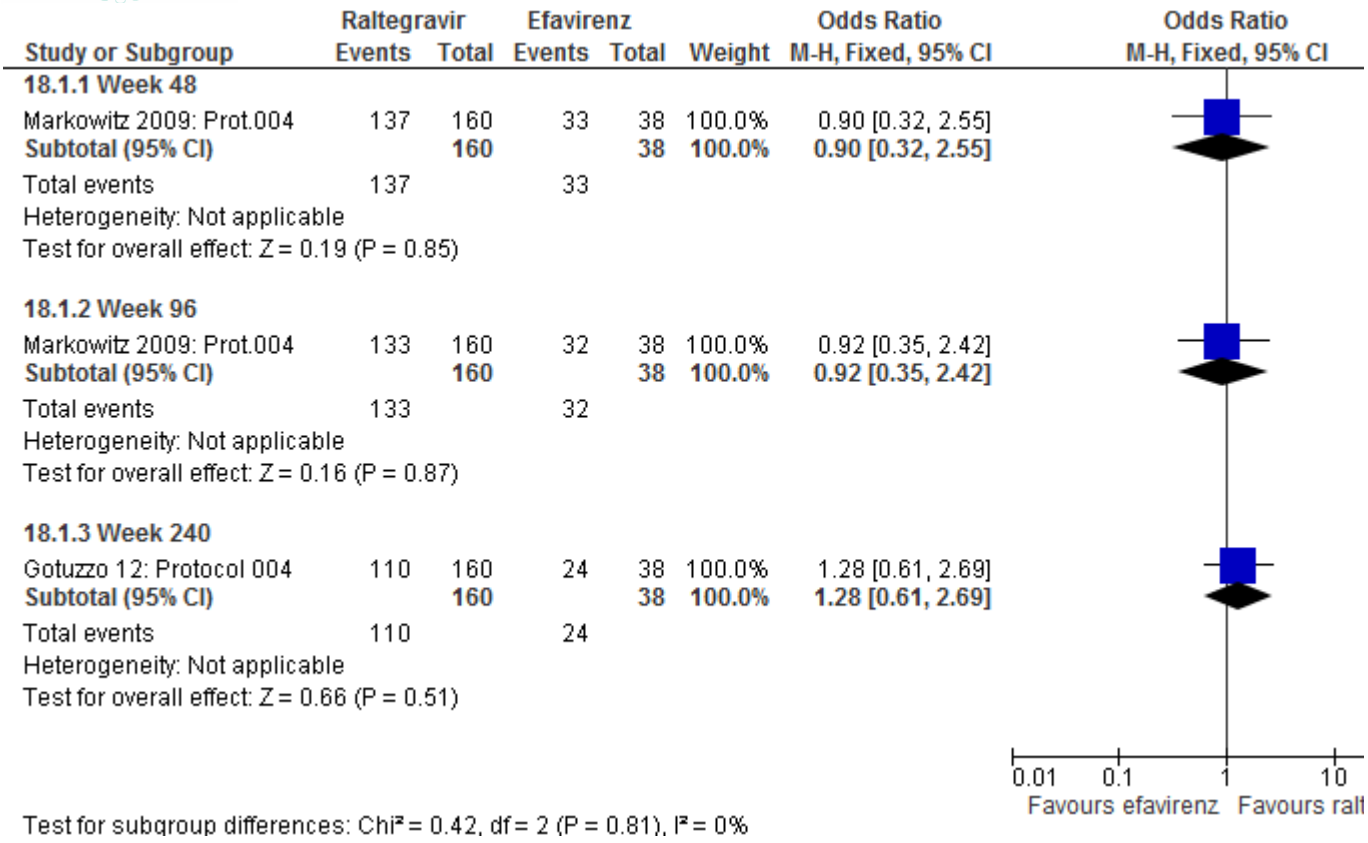
Forest plot of comparison: 17 Raltegravir + tenofovir/ emtricitabine versus efavirenz + tenofovir/ emtricitabine, outcome: 17.9 Treatment-emergent grade 3/4 abnormality in alanine aminotransferase.



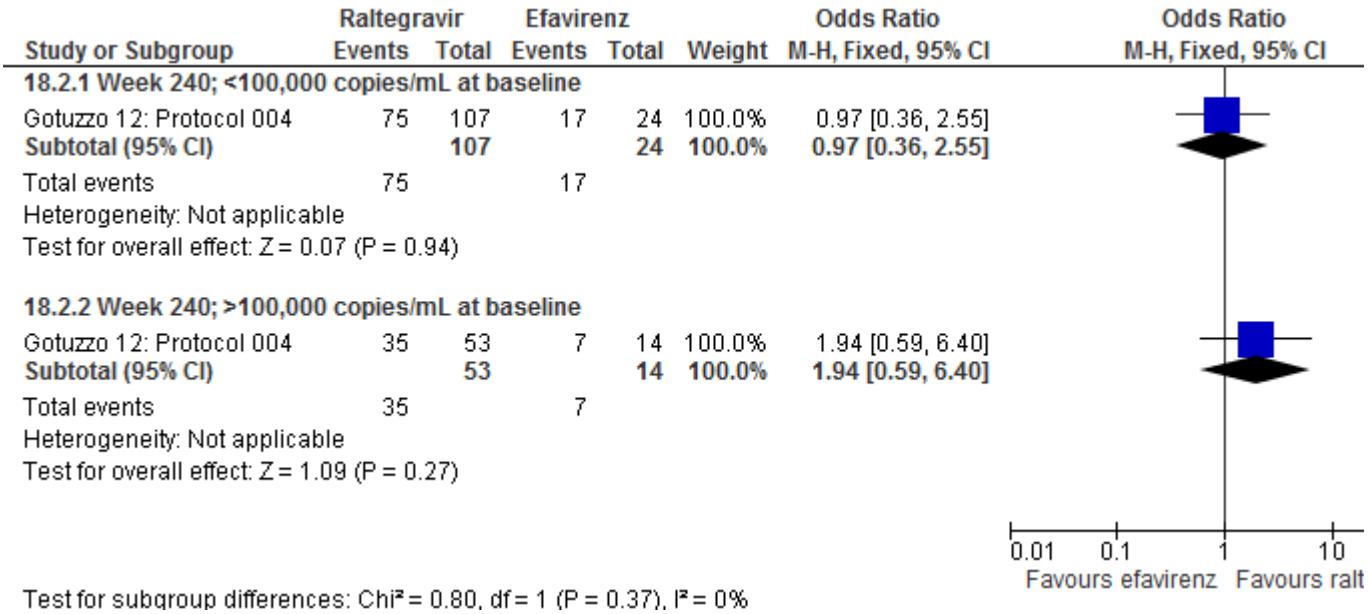
18 Raltegravir + tenofovir/ lamivudine versus efavirenz + tenofovir/ lamivudine

No new studies; later publications from Protocol 004 (study previously described in guideline).

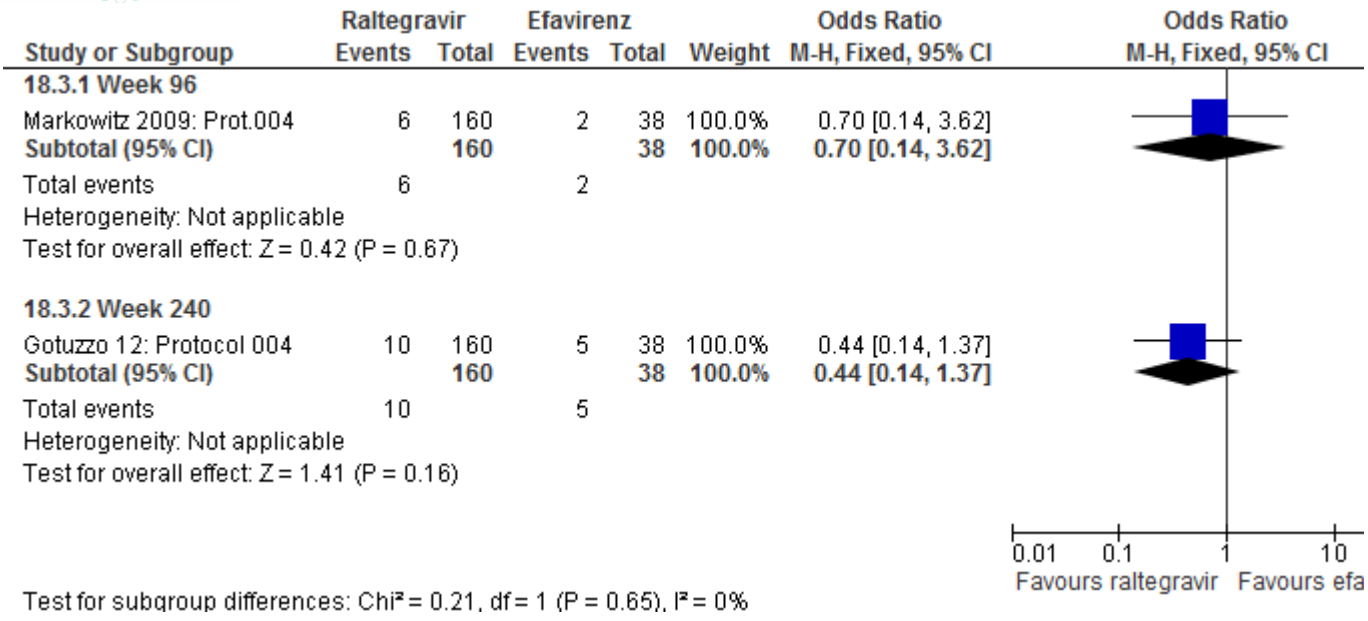
Forest plot of comparison: 18 Raltegravir + tenofovir/ lamivudine versus efavirenz + tenofovir/ lamivudine, outcome: 18.1 Virological response.



Forest plot of comparison: 18 Raltegravir + tenofovir/ lamivudine versus efavirenz + tenofovir/ lamivudine, outcome: 18.2 Virological response; subgroups.

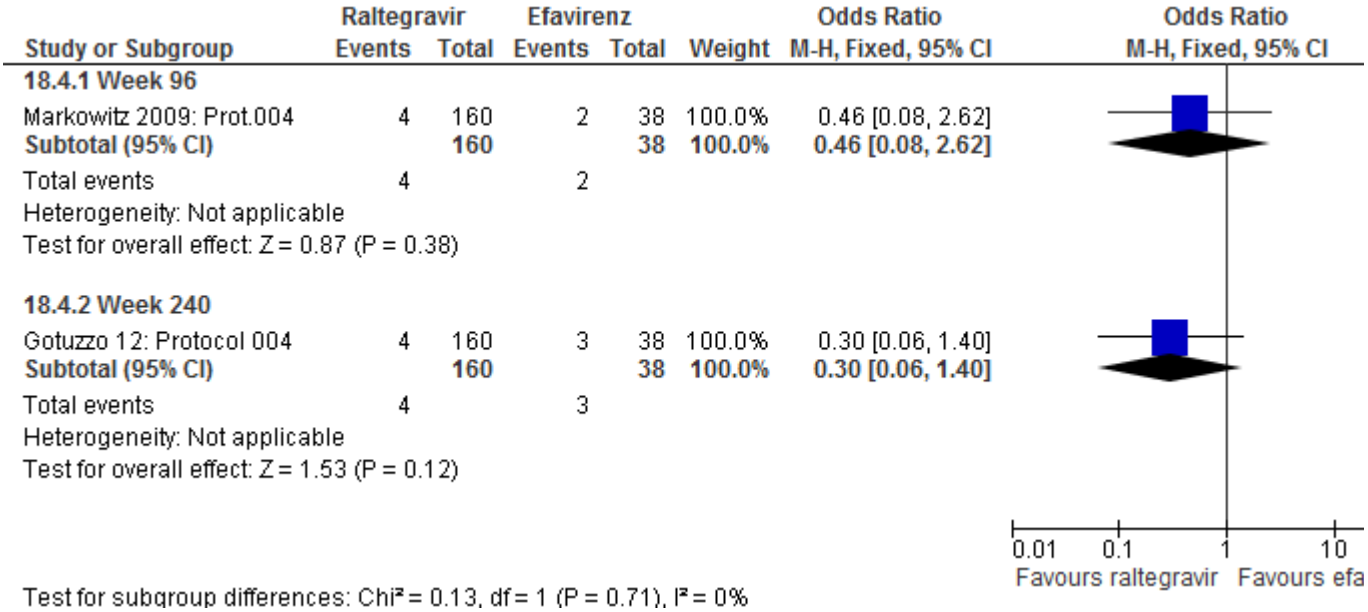


Forest plot of comparison: 18 Raltegravir + tenofovir/ lamivudine versus efavirenz + tenofovir/ lamivudine, outcome: 18.3 Virological failure.

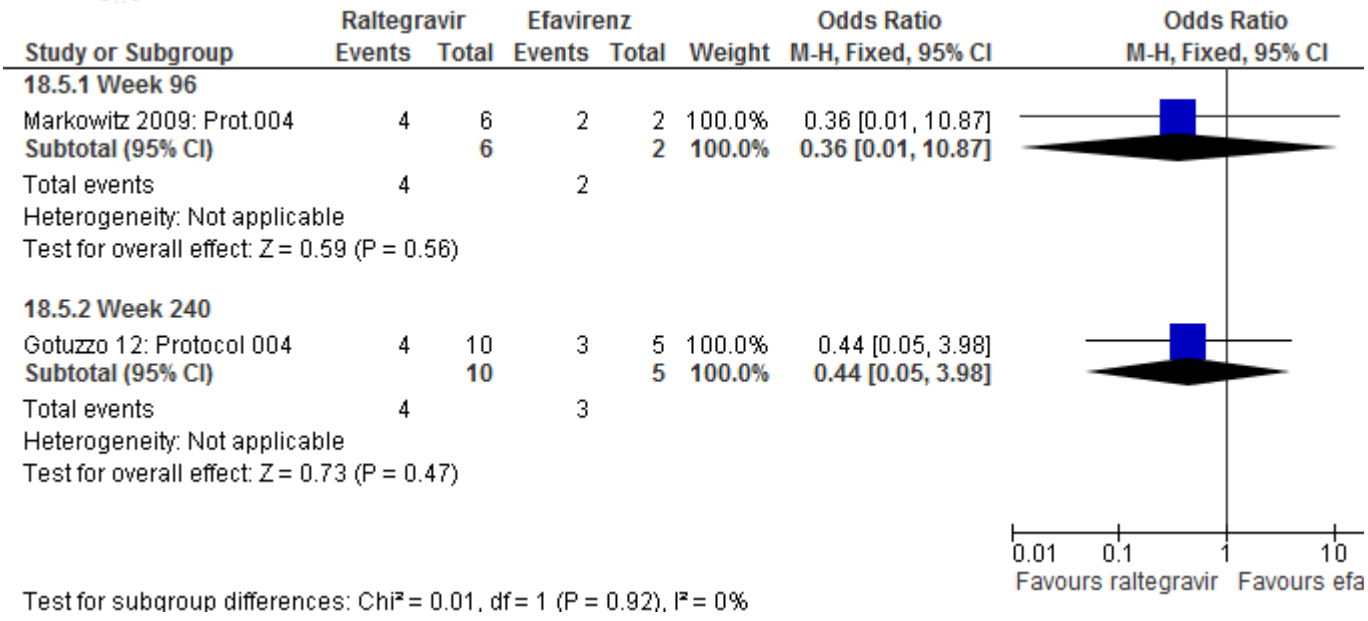


Subgroups by < or > 100,000 copies/mL not available.

Forest plot of comparison: 18 Raltegravir + tenofovir/ lamivudine versus efavirenz + tenofovir/ lamivudine, outcome: 18.4 Resistance (% total population).



Forest plot of comparison: 18 Raltegravir + tenofovir/ lamivudine versus efavirenz + tenofovir/ lamivudine, outcome: 18.5 Resistance (% of those with virological failure).



Virologic failure occurred by year 5 in 10 (6%) of 160 patients in the raltegravir group and 5 (13%) of 8 patients in the efavirenz group. Integrase genotype data were available for 8 patients who experienced virologic failure while receiving raltegravir and had sufficient virus for amplification. Signature integrase resistance mutations were demonstrated in 3 of these patients, including N155H (2 patients) and Y143C (1 patient); these 3 patients also displayed resistance to lamivudine, and one also showed resistance to tenofovir. Of the remaining 5 patients, one was resistant to lamivudine only, and 4 had no evidence of resistance to any drug in the regimen. Among the 5 patients with virologic failure on efavirenz, 2 had evidence of resistance to efavirenz, 1 showed resistance to tenofovir/lamivudine, and 2 showed no resistance to any drug in the regimen.

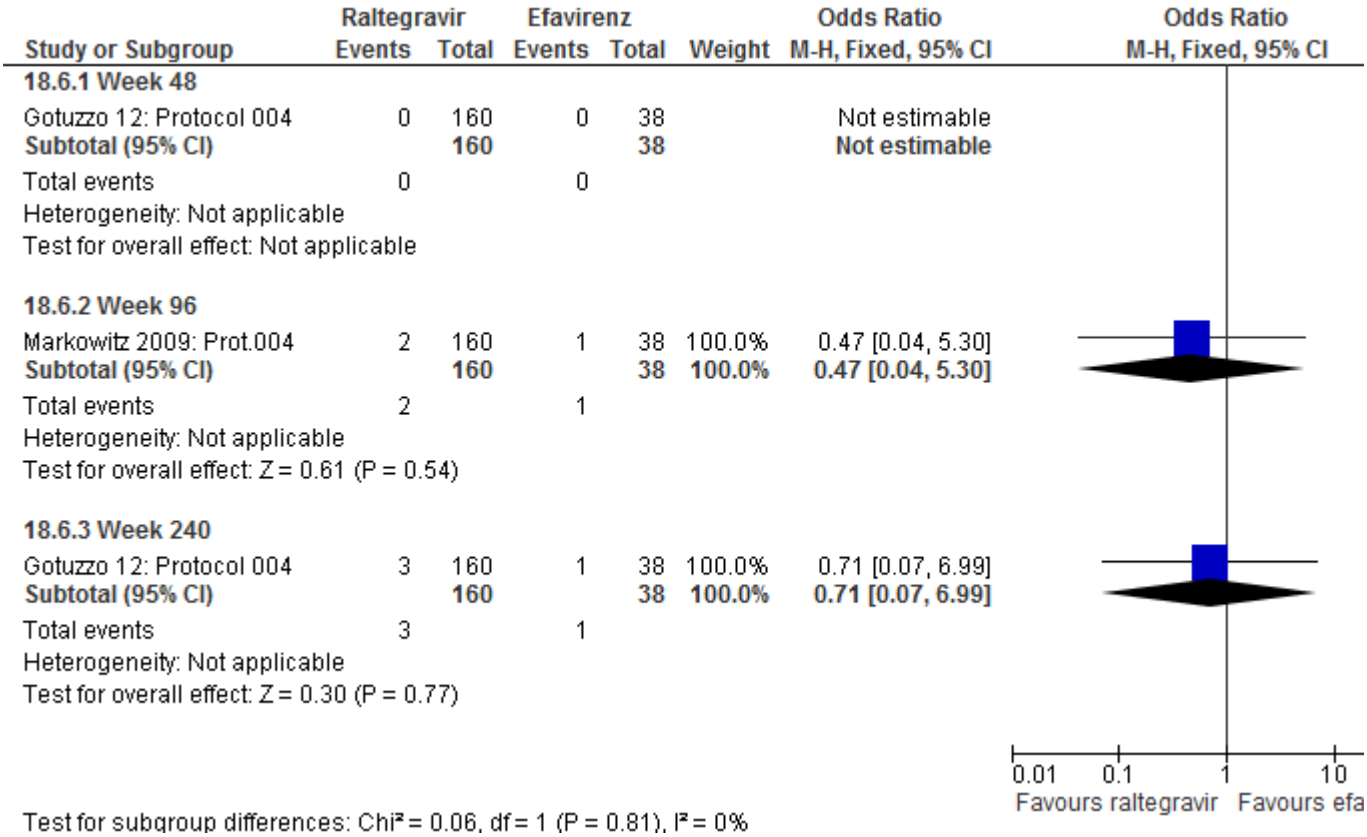
Treatment Group	**Treatment Emergent Mutations**			
	Raltegravir	Lamivudine	Tenofovir	Efavirenz
Raltegravir	N155H, V151I, L74M, L74M/L	K65K/R , M184M/I/V	K65K/R	None
	N155H	M184M/I/V	None	None
	S230R , Y143C	M184M/I/V	None	None
	None	M184V	None	None
	None	None	None	None
	None	None	None	None
	None	None	None	None

	None	None	None	None
	Not tested	None	None	None
	Not tested	None	None	None
Efavirenz	None	K65R	K65R	None
	None	K219Q , M184V	K219Q	K103K/N, Y188Y/H, Y188L
	None	None	None	Y188Y/H
	Not tested	None	None	None
	Not tested	None	None	None

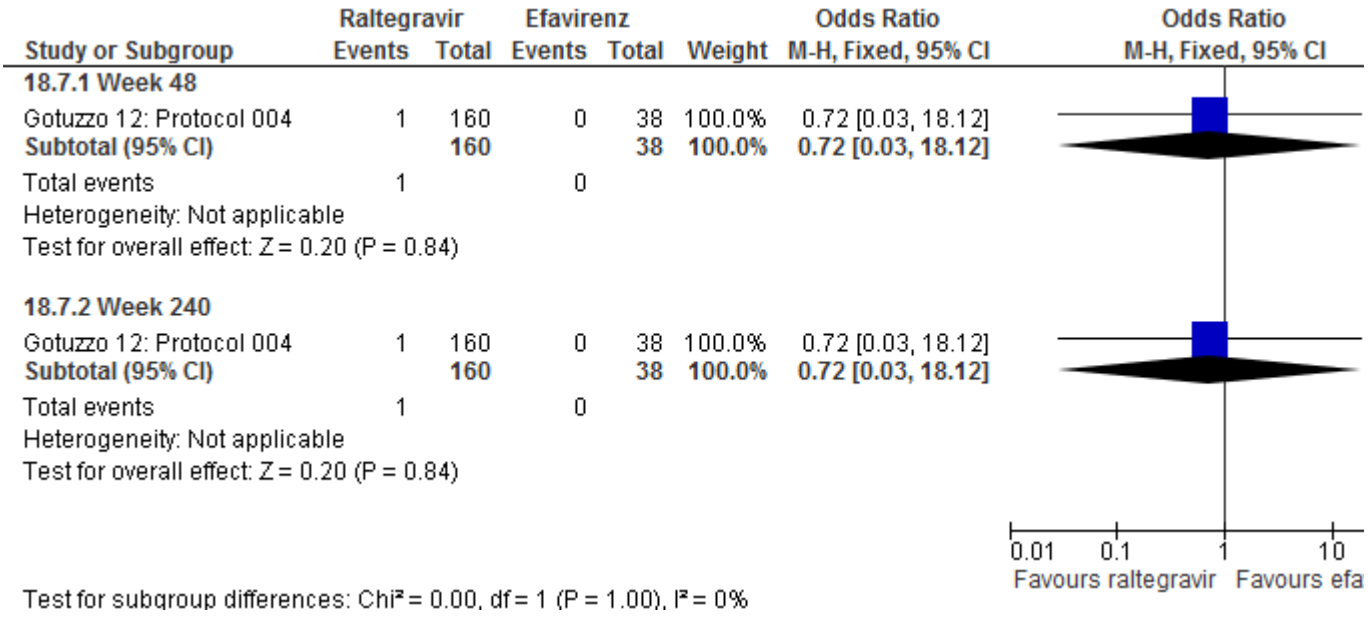
† Virologic failure (confirmed plasma HIV-1 RNA >50 copies/mL) or virologic relapse, defined as two consecutive measurements (at least one week apart) of (1) plasma HIV-1 RNA >50 copies/mL after initial response with plasma HIV-1 RNA <50 copies/mL, or (2) >1.0 log10 increase in plasma HIV-1 RNA above the nadir level. Note: the threshold for inadequate suppression in the above definition was HIV-1 RNA >400 copies/mL prior to Week 144.

‡ Patient did not have sufficient virus for amplification.

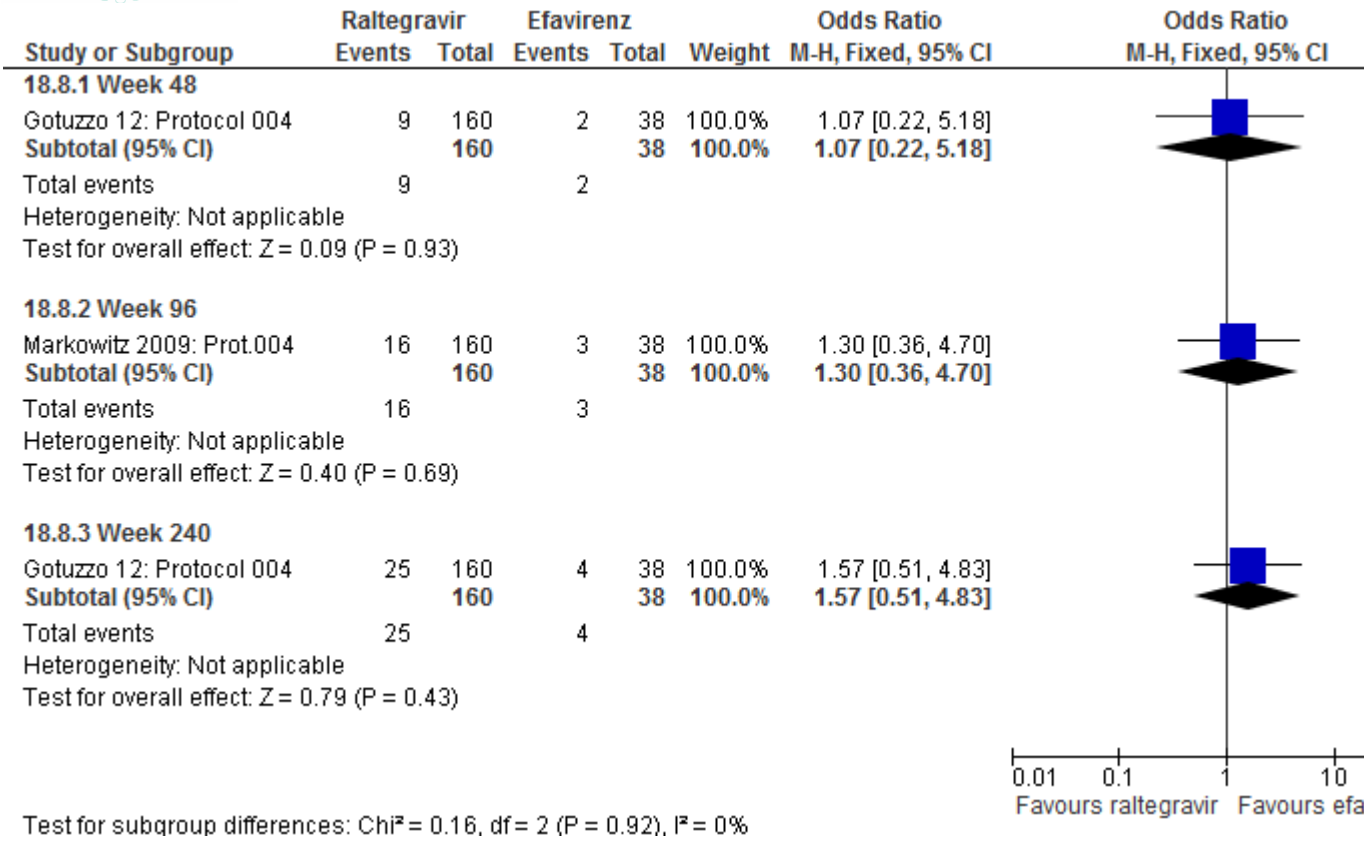
Forest plot of comparison: 18 Raltegravir + tenofovir/ lamivudine versus efavirenz + tenofovir/ lamivudine, outcome: 18.6 Discontinued because of clinical adverse events.



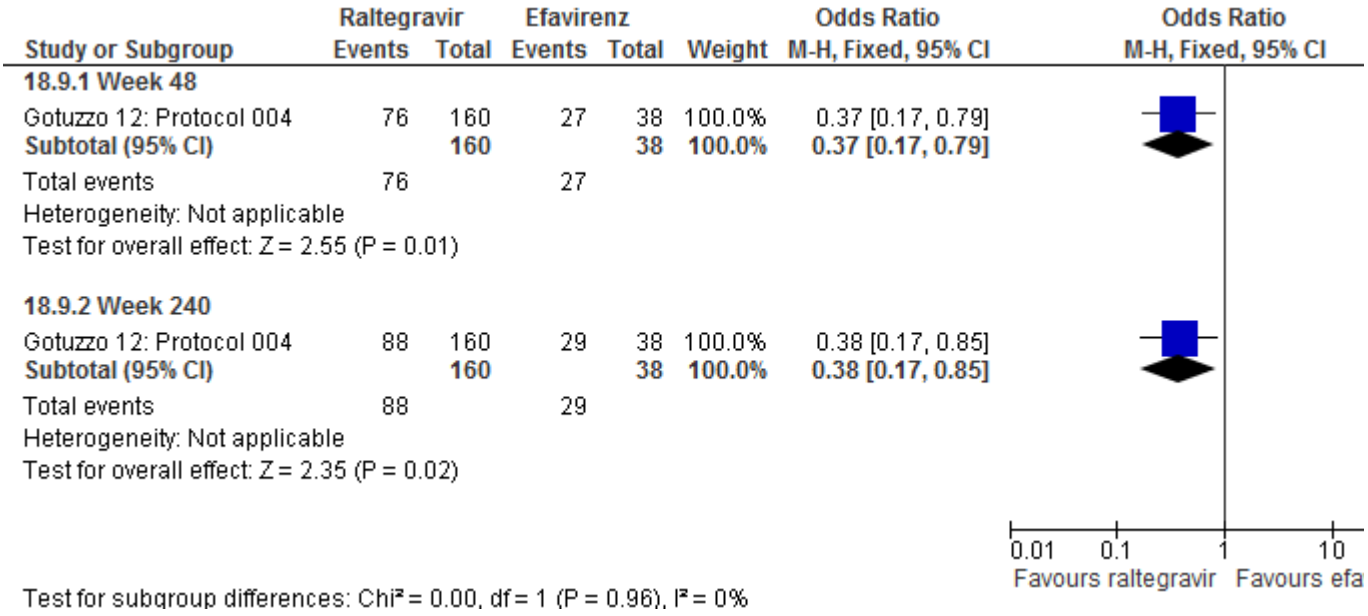
Forest plot of comparison: 18 Raltegravir + tenofovir/ lamivudine versus efavirenz + tenofovir/ lamivudine, outcome: 18.7 Discontinued due to laboratory adverse events.



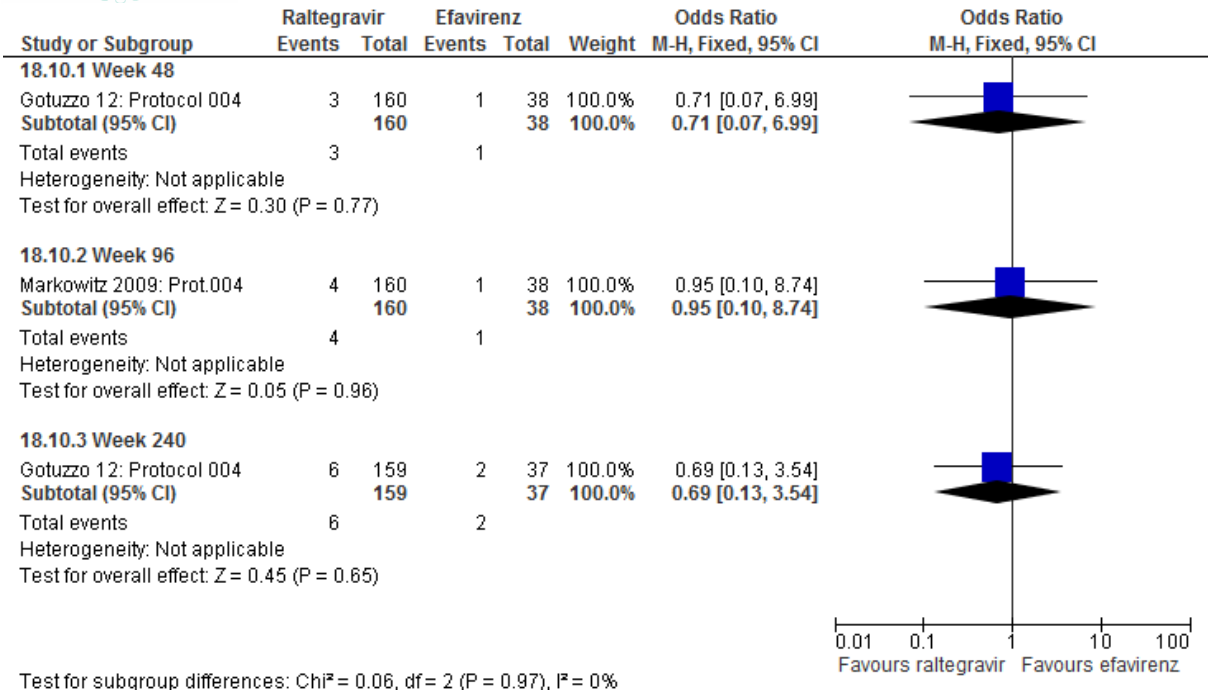
Forest plot of comparison: 18 Raltegravir + tenofovir/ lamivudine versus efavirenz + tenofovir/ lamivudine, outcome: 18.8 Serious clinical adverse events.



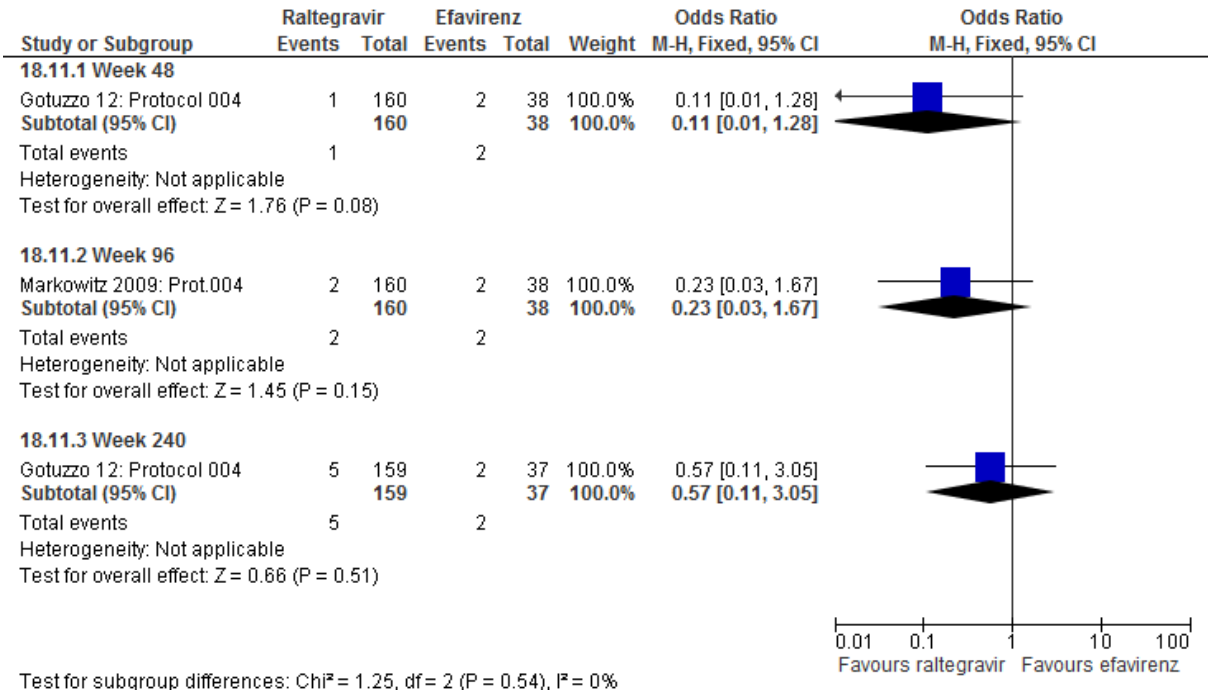
Forest plot of comparison: 18 Raltegravir + tenofovir/ lamivudine versus efavirenz + tenofovir/ lamivudine, outcome: 18.9 Drug-related clinical adverse events.



Forest plot of comparison: 18 Raltegravir + tenofovir/ lamivudine versus efavirenz + tenofovir/ lamivudine, outcome: 18.10 Grade 3 or 4 aspartate aminotransferase.



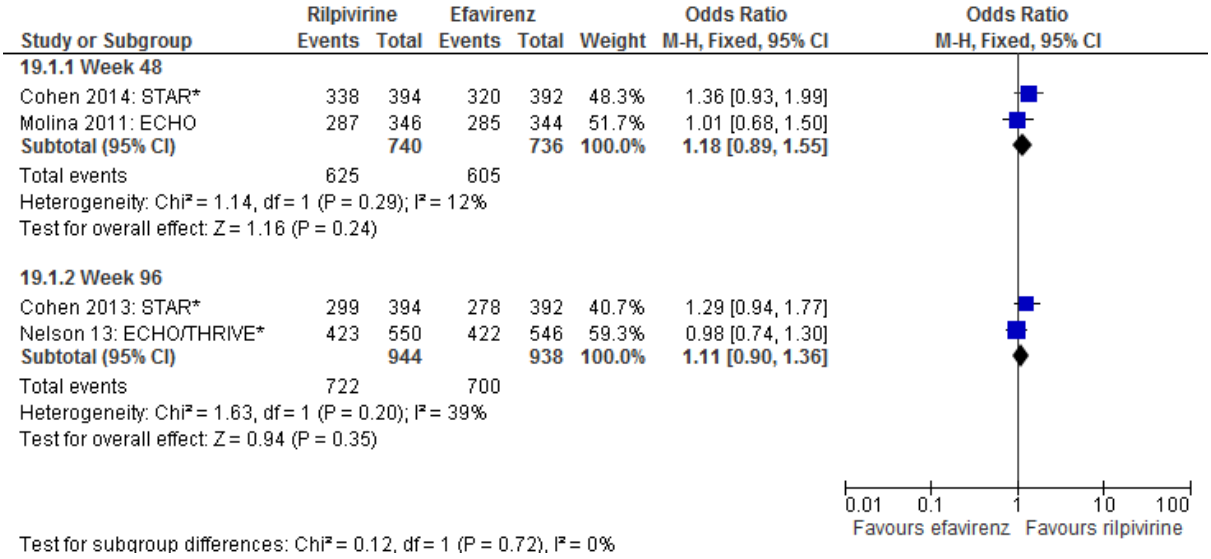
Forest plot of comparison: 18 Raltegravir + tenofovir/ lamivudine versus efavirenz + tenofovir/ lamivudine, outcome: 18.11 Grade 3 or 4 alanine aminotransferase.



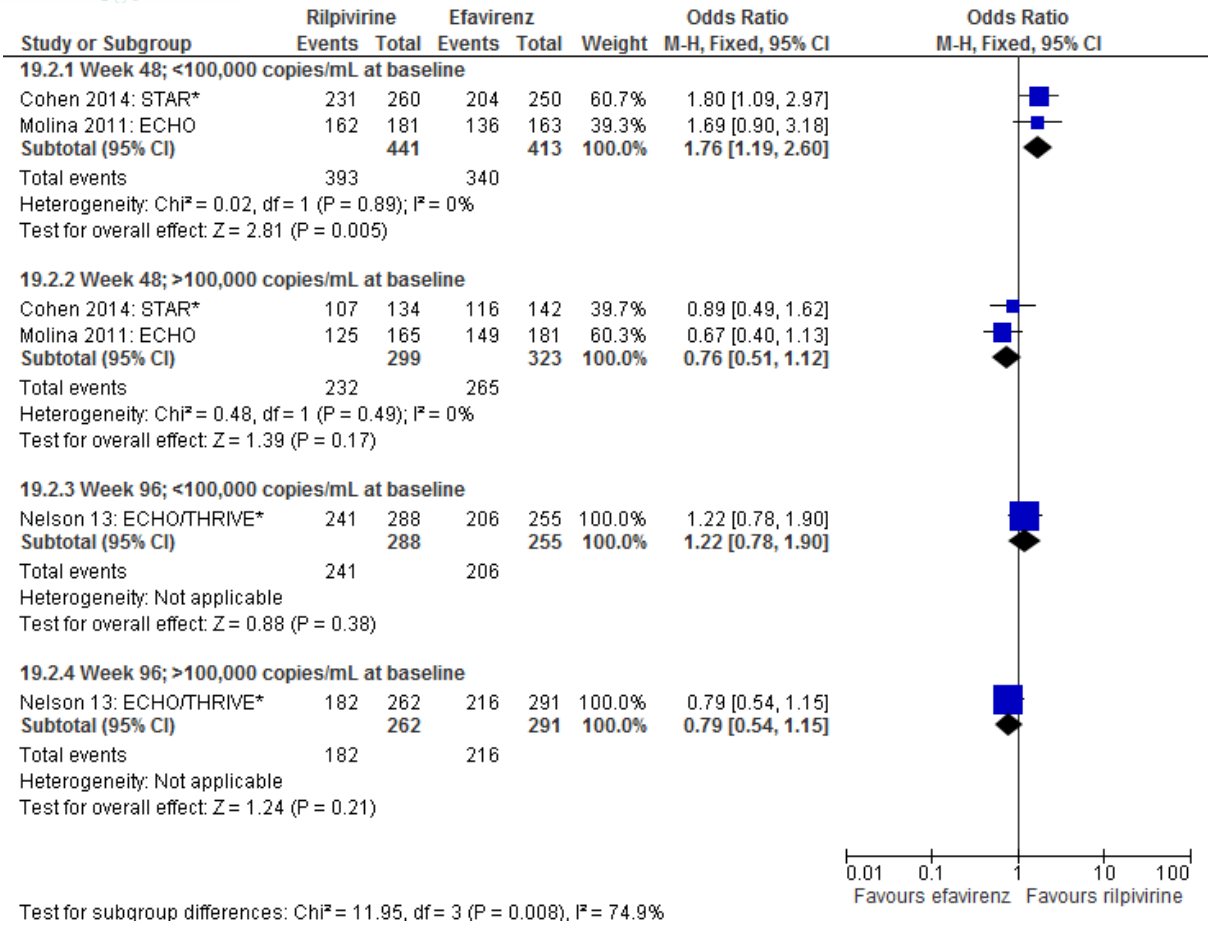
19 Rilpivirine + emtricitabine/tenofovir versus efavirenz + emtricitabine/tenofovir

ECHO, THRIVE and STAR studies included in previous guidelines.

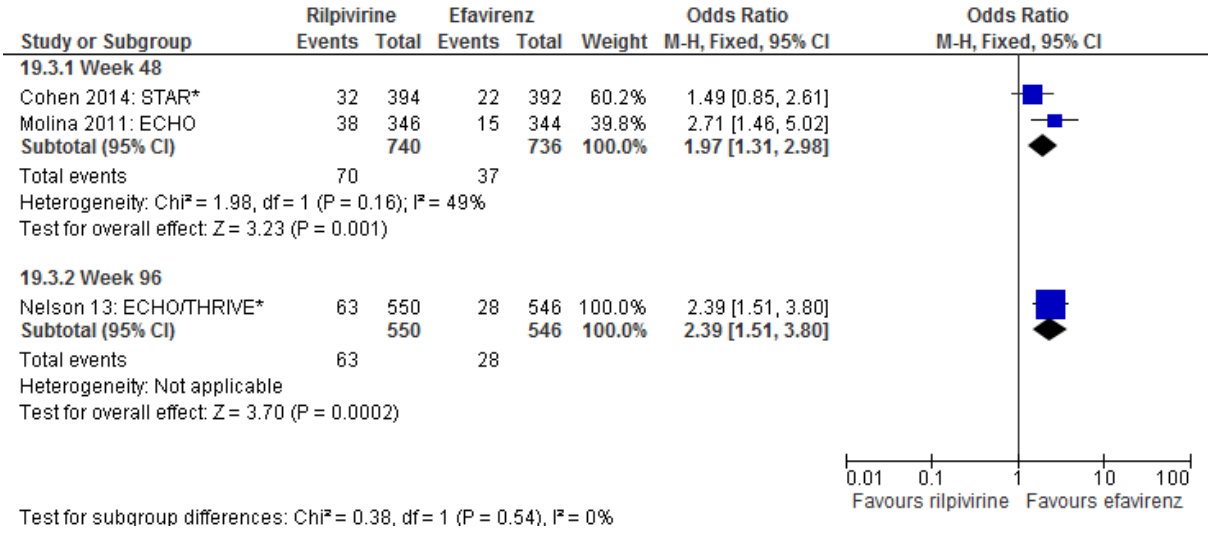
Forest plot of comparison: 19 Rilpivirine + emtricitabine/tenofovir versus efavirenz + emtricitabine/tenofovir, outcome: 19.1 HIV-1 RNA<50 copies/mL.



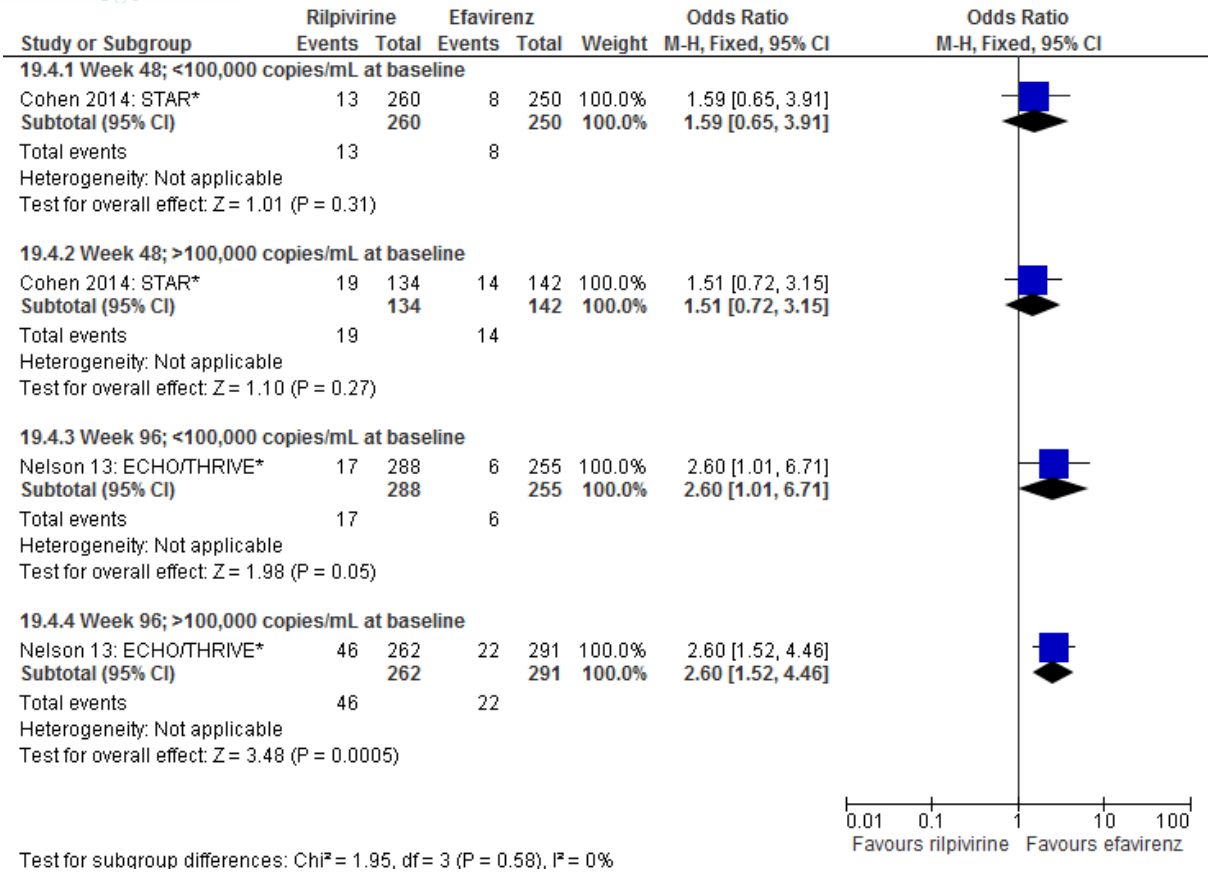
Forest plot of comparison: 19 Rilpivirine + emtricitabine/tenofovir versus efavirenz + emtricitabine/tenofovir, outcome: 19.2 HIV-1 RNA<50 copies/mL; subgroups.



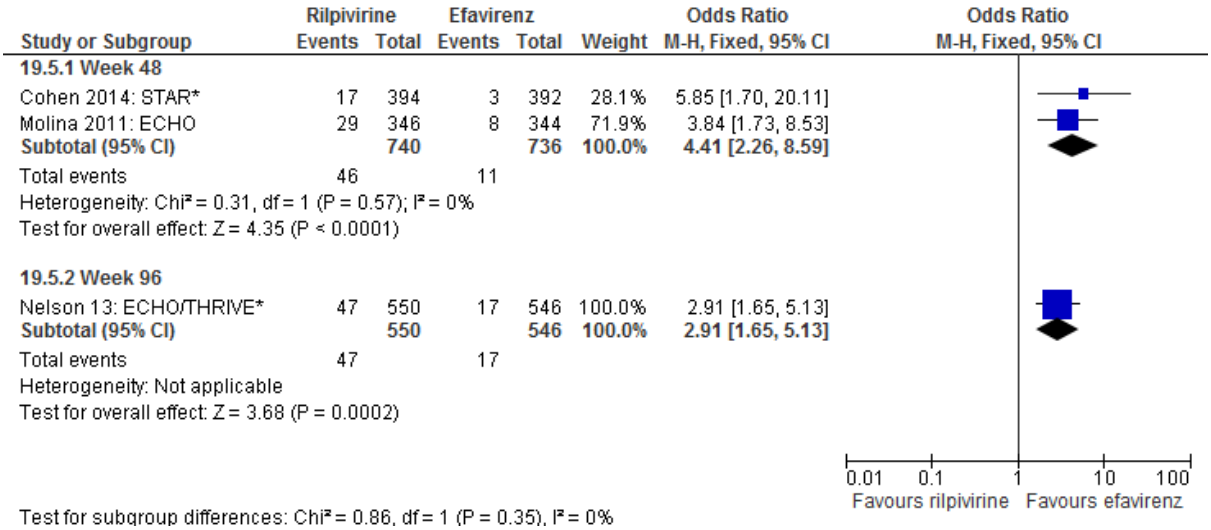
Forest plot of comparison: 19 Rilpivirine + emtricitabine/tenofovir versus efavirenz + emtricitabine/tenofovir, outcome: 19.3 Virological failure.



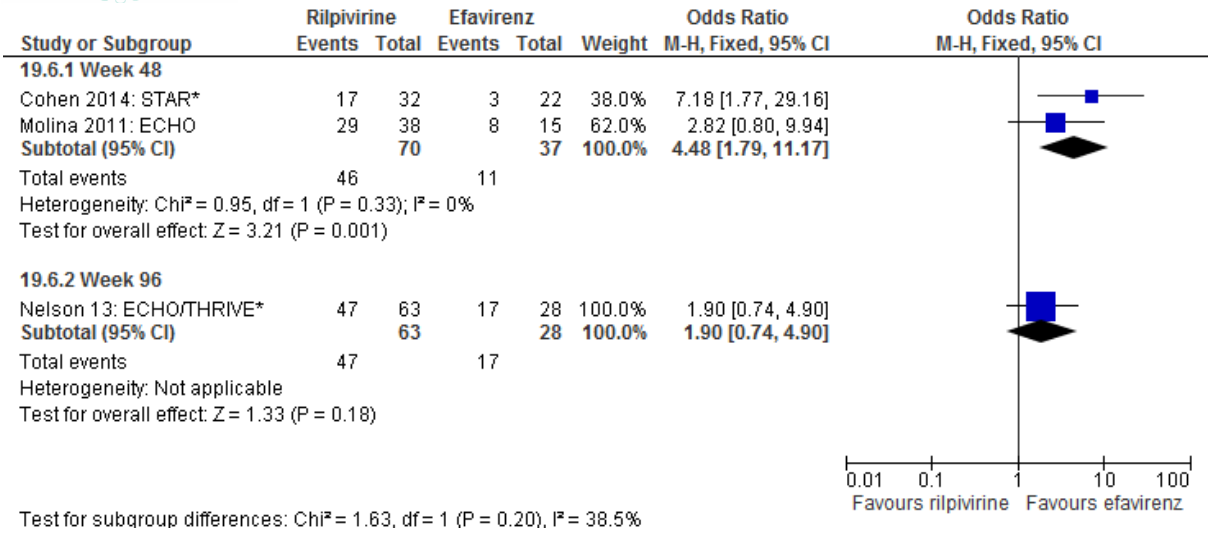
Forest plot of comparison: 19 Rilpivirine + emtricitabine/tenofovir versus efavirenz + emtricitabine/tenofovir, outcome: 19.4 Virological failure; subgroups.



Forest plot of comparison: 19 Rilpivirine + emtricitabine/tenofovir versus efavirenz + emtricitabine/tenofovir, outcome: 19.5 Resistance (% total population).



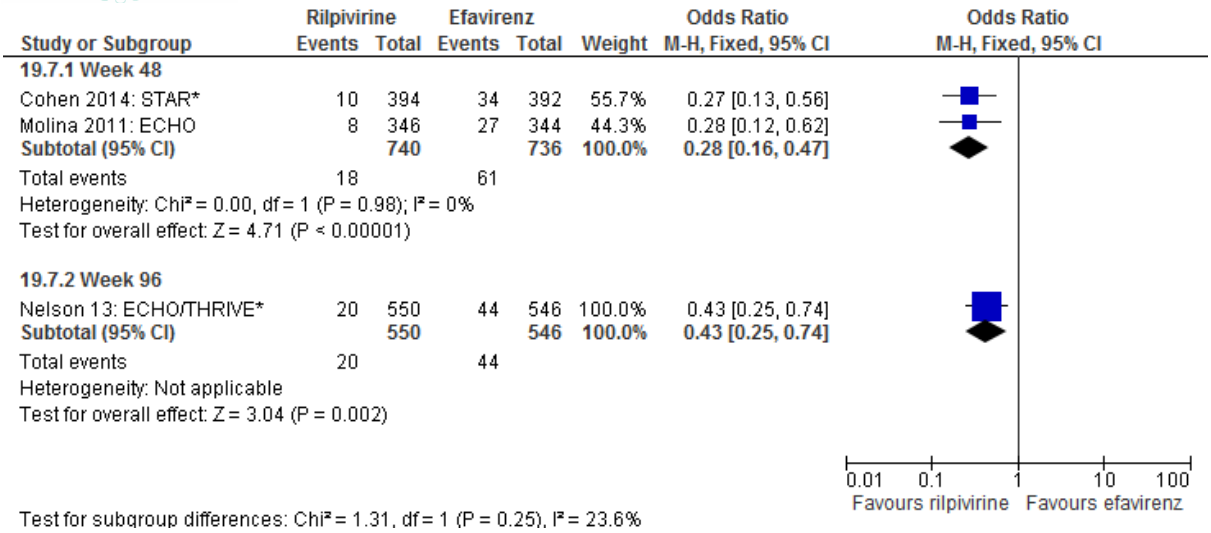
Forest plot of comparison: 19 Rilpivirine + emtricitabine/tenofovir versus efavirenz + emtricitabine/tenofovir, outcome: 19.6 Resistance (% of those with virological failure).



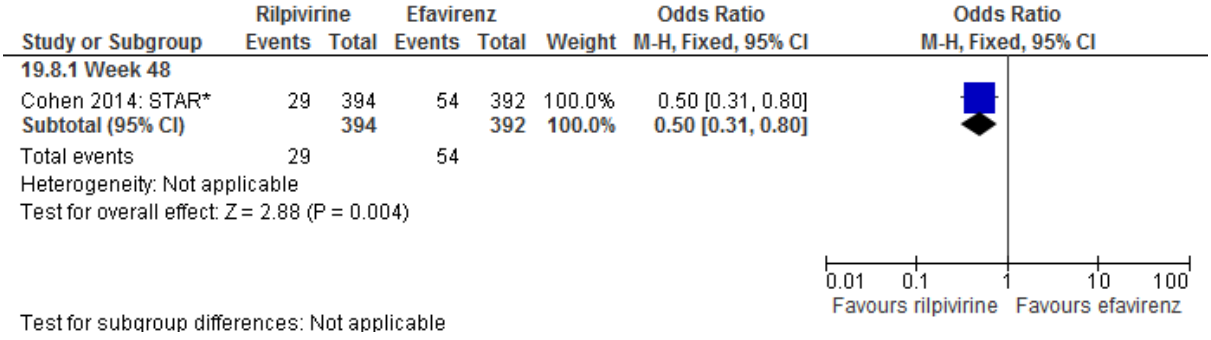
Cohen 2014: STAR at 48 weeks: Inclusion in the resistance analysis population (RAP) required at least 8 weeks of treatment on study drug and HIV-1 RNA at least 400copies/ml at the time of analysis, as this is the minimum viral concentration needed for the PhenoSense GT assay. The RAP consisted of 20 participants in the RPV/FTC/TDF arm and seven participants in the EFV/FTC/TDF arm. There were 12 participants in the RPV/FTC/TDF arm and 16 in the EFV/FTC/TDF arm who were virologic failures at week 48, but were not included in the RAP because they did not meet the 400copies/ml threshold or had been treated less than 8 weeks. In the RPV/FTC/TDF arm, 4% (17 of 394 treated patients; 85% of RAP) had emergent key primary NNRTI and/or NRTI resistance-associated mutations [(NNRTI-R): Y181C/I (n=8), E138K/Q (n=6), K101E (n=5); (NRTI-R): M184V/I (n=15), K65R/N (n=3)]. Of these 17 RPV/FTC/TDF-treated participants, 16 had both RPV and FTC resistance-associated substitutions. Fifteen isolates had cross-resistance to another NNRTI, but eight of these remained phenotypically susceptible to EFV. In the EFV/FTC/TDF arm, 1% (three of 392 treated patients; 43% of RAP) had emergent resistance [NNRT-R: K103N (n=1), G190E/Q (n=1), and Y188L (n=1); NRTI-R: M184I (n=1)].

Nelson 2013: ECHO/THRIVE at week 96: Through 96 weeks, a similar proportion of subjects in both groups with virologic failure in the resistance analysis developed NNRTI mutations (55% in the RPV group and 50% in the EFV group). However, a greater proportion developed NtRTI mutations with RPV+FTC/TDF (58%) than with EFV+FTC/TDF (27%) The most frequently occurring NtRTI resistance-associated mutation in both groups was M184I. The most frequently occurring NNRTI resistance-associated mutations were E138K (RPV group) and K103N (EFV group). The mutations E138K and M184I were the most common mutations observed together in the RPV+FTC/TDF group.

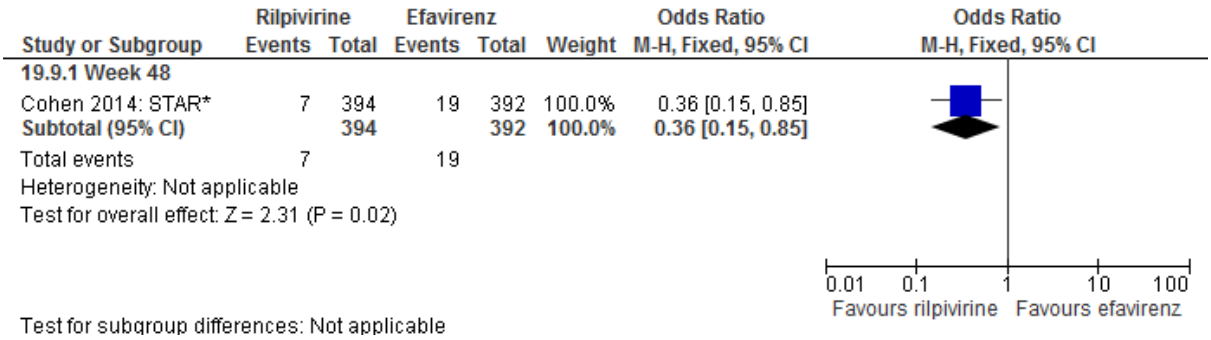
Forest plot of comparison: 19 Rilpivirine + emtricitabine/tenofovir versus efavirenz + emtricitabine/tenofovir, outcome: 19.7 Discontinued due to adverse event or death.



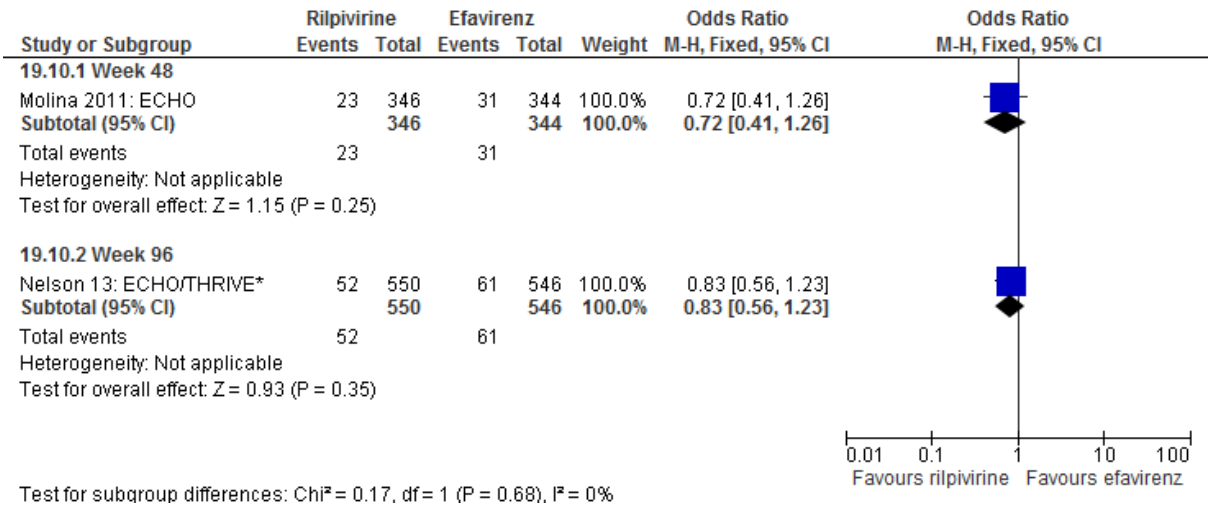
Forest plot of comparison: 19 Rilpivirine + emtricitabine/tenofovir versus efavirenz + emtricitabine/tenofovir, outcome: 19.8 Grade 3 or 4 treatment-emergent adverse event (clinical).



Forest plot of comparison: 19 Rilpivirine + emtricitabine/tenofovir versus efavirenz + emtricitabine/tenofovir, outcome: 19.9 Grade 3 or 4 treatment-emergent adverse event (clinical) related to study drug.



Forest plot of comparison: 19 Rilpivirine + emtricitabine/tenofovir versus efavirenz + emtricitabine/tenofovir, outcome: 19.10 Serious adverse event (clinical).



No new data on grade 3-4 laboratory events, AST/ALT, rash or diarrhoea.