

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



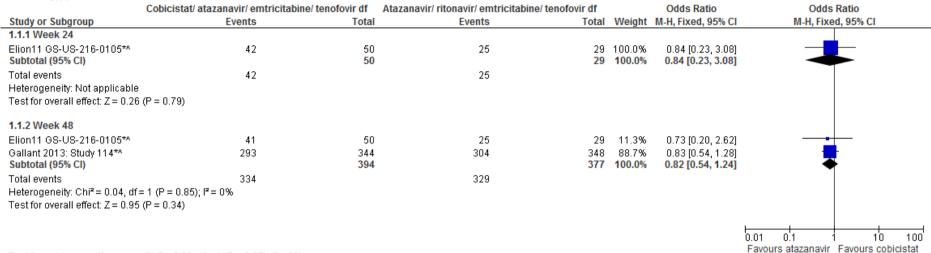
atazanavir	demographics and disease characteristics were		mutations (International AIDS	emtricitab	emtricitab		normal	
and fixed-	similar between treatment groups.		Society - U.S.A. guidelines),	ine/	ine/		approximation	
dose			normal ECG, estimated	tenofovir	tenofovir		methods, stratified	
emtricitabine/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



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

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



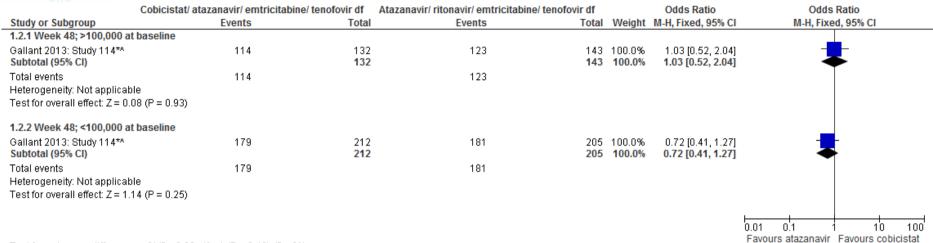


Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%

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

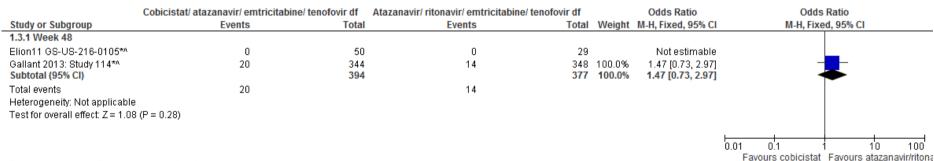
1 Cobicistat/ atazanavir/ emtricitabine/ tenofovir df versus atazanavir/ ritonavir/ emtricitabine/ tenofovir df, outcome: 1.2 HIV RNA <50 copies/mL; subgroups.





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.

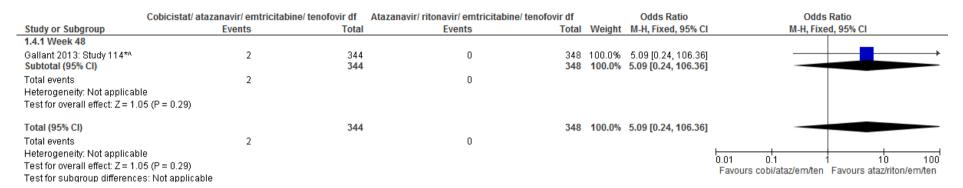


Test for subgroup differences: Not applicable

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).



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

C	Cobicistat/ atazanavir/ emtricitabine/	tenofovir df A	tazanavir/ ritonavir/ emtricitabine/ tenol	ovir df		Odds Ratio	Odds R	atio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed,	95% CI
1.5.1 Week 48								
Gallant 2013: Study 114*A Subtotal (95% CI)	2	20 20	0		100.0% 100.0%	3.92 [0.17, 88.15] 3.92 [0.17, 88.15]		
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.86	2 (P = 0.39)		0					
Total (95% CI)	2	20	0	14	100.0%	3.92 [0.17, 88.15]		
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.86 Test for subgroup differences:	(P = 0.39)		0				0.01 0.1 1 Favours cobi/ataz/em/ten F	10 100 avours ataz/riton/em/ten



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/ emtricitabin	e/ tenofovir df	Atazanavir/ ritonavir/ emtricitabine/	tenofovir df		Odds Ratio		Odd	ds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	xed, 95% C	1	
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*^ Subtotal (95% CI)	25	344 394	25	348 377	95.0% 100.0 %	1.01 [0.57, 1.80] 1.02 [0.58, 1.79]		-	•		
Total events Heterogeneity: Chi² = 0.01, df Test for overall effect: Z = 0.07			26								
							0.01 Favou	0.1 rs cobicista	1 at Favours	10 ataza	100 anavir

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).

Co	obicistat/ 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
1.7.1 Week 48							
Elion11 GS-US-216-0105*^ Subtotal (95% CI)	2	50 50	1		100.0% 100.0 %	1.17 [0.10, 13.46] 1.17 [0.10, 13.46]	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.12 (P	2 = 0.90)		1				
							0.01 0.1 1 10 100 Favours cobicistat Favours atazanavir



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/ ten	ofovir df		Odds Ratio		Odds Rat	io	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Γ	M-H, Fixed, 9	5% 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** Subtotal (95% CI)	225	344 394	197	348 377	91.6% 100.0%	1.45 [1.07, 1.97] 1.50 [1.12, 2.00]		•		
Total events Heterogeneity: Chi² = 0.43, df Test for overall effect: Z = 2.71			210							
							0.01 0.1 Favours co	obicistat Fav	10 vours ataz	100 zanavir

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.

С	Cobicistat/ atazanavir/ emtricitabine/	tenofovir df	Atazanavir/ ritonavir/ emtricitabine	tenofovir df		Odds Ratio		Odd	s Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% C	1	
1.9.1 Week 48											
Gallant 2013: Study 114*^ Subtotal (95% CI)	10	344 344	7	348 348	100.0% 100.0%	1.46 [0.55, 3.88] 1.46 [0.55, 3.88]		-			
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.76	10 (P = 0.45)		7								
T-16							0.01 Favo	0.1 ours cobicista	1 t Favours	10 atazan	100 avir/ritona

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.

Col	bicistat/ atazanavir/ emtricitabin	e/ tenofovir df /	Atazanavir/ ritonavir/ emtricitabin	e/ tenofovir df		Odds Ratio		Odds	s Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% C	1	
1.10.1 Week 48											
Gallant 2013: Study 114*A Subtotal (95% CI)	11	344 344	7	348 348	100.0% 100.0%	1.61 [0.62, 4.20] 1.61 [0.62, 4.20]		-			
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.97 (P	11 = 0.33)		7								
							0.01	0.1	1	10	100
T 16 1 100 N							Fav	ours cobicistat	Favours	atazan	avir/ritona

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



	who discontinued prior to week 48, two withdrew		lower; evidence of				biomarkers	
	consent, one was noncompliant, one was lost to		significantly decreased				(fibrinogen, d	
	follow-up, and one relocated. Of six (19.4%)		hepatic function or				-dimer), and the	
	subjects in the ATV/r arm who discontinued early,		decompensation; presence of				microbial	
	two discontinued due to AEs (one with grade 3		any Centers				translocation	
	leukocytoclastic vasculitis and one with grade 1		for Disease Control and				biomarker	
	increased blood creatinine), one discontinued due		Prevention active AIDS-				lipopolysaccharide.	
	to pregnancy, one discontinued because of		defining illness (Category C					
	investigational product dispensing error, one was		conditions), except stable					
	lost to follow-up, and one withdrew consent.		cutaneous Kaposi's sarcoma					
	·		or wasting syndrome; acute					
	Setting: Multi-centre (USA)		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.					
Jeffrey L.	RCT: phase 3, open-label study randomized in a	1809	Inclusion: adults infected	Darunavir	Atazanavir	96	The primary	National
Lennox et al	1:1:1 ratio with follow-up for at least 96 weeks.		with HIV-1 receiving care in	800 mg/d,	300 mg/d,	wee	objective was to	Institute of
for the ACTG	(ClinicalTrials.gov: NCT00811954)		the United States and Puerto	with	with	ks	evaluate regimen	Allergy and



A5257 Team.		Rico with plasma HIV-1 RNA	ritonavir,	ritonavir,	equivalence	Infectious
	Pandomication, permuted blocks stratified	•			•	
Efficacy and Tolerability of	Randomisation: permuted blocks stratified according to the HIV-1 RNA level (>100 000 vs.	levels greater than 1000 copies/mL who had received	100 mg/d, plus	100 mg/d (n=605);	regarding virologic efficacy and	Diseases.
3	4100 000 copies/mL) with balancing by institution.	10 or fewer days of	combinatio	or a third	tolerability over 96	
Nonnucleosid					-	
	To ensure treatment balance by cardiovascular risk	antiretroviral therapy.	n	group	weeks. Virologic	
e Reverse	for an embedded cardiovascular substudy,	Participants had documented	emtricitabin	received	failure was defined	
Transcriptase	randomization was stratified by intent to	absence of genotypic	e, 200	raltegravir	as a confirmed HIV-	
Inhibitor-	participate in the substudy and 10-year	resistance to nucleoside	mg/d,	400 mg	1 RNA level greater	
Sparing	Framingham risk for myocardial infarction or	reverse transcriptase	and	twice	than 1000	
Antiretroviral	coronary death (<6% vs. >6%).	inhibitors and Pis; integrase	tenofovir	daily	copies/mL at or	
Regimens for		genotyping was not required	disoproxil	(n=603),	after 16 weeks and	
Treatment-	Allocation concealment: Not stated	because transmitted	fumarate,	plus	before 24 weeks	
Naive		integrase resistance is rare.	300 mg/d	combinati	from randomization	
Volunteers	Blinding: No: open label	The CD4+ cell count at entry	(n=601)	on	or less than 200	
Infected With		was not limited.		emtricitab	copies/mL at or	
HIV-1. A	Comparable groups at baseline: Demographic			ine, 200	after 24 weeks. The	
Randomized,	characteristics of the population were	Exclusion: Not stated		mg/d,	primary tolerability	
Controlled	well-balanced among the 3 groups			and	end point was the	
Equivalence				tenofovir	time from	
Trial.	Sample size calculation: The target sample size of			disoproxil	randomisation to	
Ann Intern	600 participants per group would provide 90%			fumarate,	discontinuation of	
Med. 2014;	power to show equivalence in pairwise regimen			300 mg/d.	the randomised	
161: 461-471.	comparisons, assuming rates of virologic failure,				regimen	
doi:10.7326/	tolerability failure, and loss to follow-up of 25%,				component for	
M14-1084	10%, and 12%, respectively.				toxicity (per-site	
					attribution);	
					treatment	
	Intention to treat analysis: Yes				discontinuation for	
					other reasons were	
	Drop out: 13% lost to follow up, or unable to travel				considered	
	to clinic, or non-compliant for other reason				competing events.	
					Substitution of any	
	Setting: 57 sites in the United States and Puerto				component of the	
	Rico				fixed-dose	
					combination of TDF	
					plus emtricitabine	
					was not considered	
					tolerability failure.	
					A preplanned composite end	



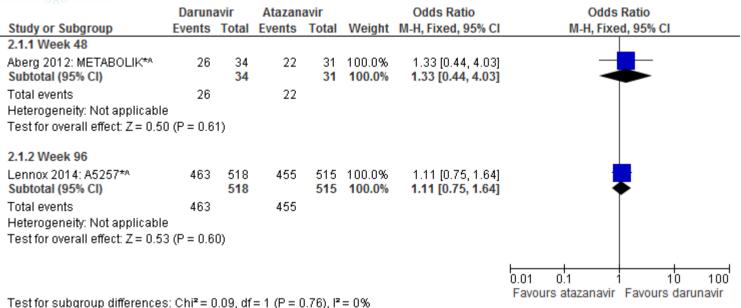
000				1				1
							point was defined	
							as the earlier	
							occurrence of	
							virologic or	
							tolerability failure.	
							The authors also	
							analyzed the	
							composite U.S.	
							Food and Drug	
							Administration	
							(FDA) end point of	
							time to loss of	
							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	Design: Multicentre, randomized, clinical trial	180	Inclusion: otherwise clinically	Darunavir	Atazanavir	96	The primary	Supported
al on behalf of	(ATADAR Study, NCT01274780)	randomi	stable HIV-infected patients	800 mg	300 mg	wee	endpoint of the	in part by
the ATADAR		sed	aged 18 years or older who	(two 400	(one pill)/	ks	ATADAR study was	research
Team.	Randomisation: A random sequence was		had never received any ART	mg pills)/	ritonavir		the mean change in	grants
Metabolic	generated by a computer using blocks of variable		and had a plasma HIV RNA	ritonavir	100 mg		total cholesterol at	from
effects of	size that were balanced at each site, stratifying by		≥1000 copies/mL. A negative	100 mg (one	(one pill)		24 weeks.	Bristol-
atazanavir/	total to high-density lipoprotein (HDL) cholesterol		urine pregnancy test within	pill) plus the	plus the		Secondary	Myers
ritonavir vs	ratio < 4.5 or ≥ 4.5.		10 days prior to study	fixed-dose	fixed-dose		endpoints were	Squibb and
darunavir/			initiation was also required	combinatio	combinati		mean changes in	Janssen-
ritonavir in	Allocation concealment: Randomization was		for participating women of	n TDF/ FTC	on TDF/		lipids other than	Cilag, and
combination	centralised.		childbearing age.	(one pill)	FTC (one		total cholesterol	Red
with				once daily	pill) once		(triglycerides, LDL	Temática
<u> </u>	<u> </u>	l		·	<u> </u>		, , ,	l .



			(00)	1 1	1	
tenofovir/	Blinding: No: open label	Exclusion criteria were	(n=89)	daily	and HDL	Cooperativ
emtricitabine		alanine or aspartate amino-		(n=91)	cholesterol, and	a de
in anti-	Comparable groups at baseline: There were no	transferase ≥ 200 mg/dL (5			total to HDL	Investigaci
retroviral-	differences in baseline characteristics between the	times the upper normal			cholesterol ratio),	ón en SIDA
naïve patients	arms.	limit), creatinine ≥ 2.6 mg/dL			insulin resistance	G03/173
(ATADAR		(2 times the upper normal			[measured using	(RIS-
Study).	Sample size calculation: Because the difference in	limit), diabetes mellitus			homeostatic model	EST11),
Journal of the	total cholesterol change between patients	defined by standard			assessment	Ministerio
International	assigned to LPV/r and patients assigned to ATV/r in	laboratory criteria or by the			(HOMA-IR)], total	de
AIDS Society	the CASTLE study was 21 mg/dL, the authors	use of anti-diabetic agents,			bilirubin, estimated	Sanidad,
2012, 15	estimated that 75 patients per arm would be	obesity defined as a body			glomerular filtration	Servicios
(Suppl 4):	needed to detect a difference equal to or higher	mass index ≥ 30 kg/m2, use			rate [calculated	Sociales e
18202	than that in plasma cholesterol if such a difference	of drugs known to affect lipid			using the	Igualdad,
	between arms exists, with 80% power and 5%	or glucose metabolism within			Modification of Diet	Spain
Martinez, E et	bilateral significance. Assuming that up to 15% of	1 month prior to inclusion,			in Renal Disease	
al for the	patients could be lost to follow-up, the sample size	any AIDS-defining event			(MDRD) study	
ATADAR	was finally set at 90 patients per arm.	requiring parenteral therapy,			equation], and CD4	
Study Group.		hypersensitivity to or			and CD8 cell counts,	
Early lipid	Intention to treat analysis: Yes	contraindication for any			the proportion of	
changes with		study drug, and pregnancy or			patients with	
atazanavir/	Drop out: 10 protocol violation, lost to follow up or	lactation at inclusion or			confirmed plasma	
ritonavir or	consent withdrawn	expectancy to become			HIV RNA > 50	
darunavir/		pregnant during follow-up.			copies/mL, and the	
ritonavir.	Setting: 16 centres in Spain				proportion of	
HIV Medicine					patients with study	
(2014), 15,					drug	
330–338					discontinuation	
					because of adverse	
					effects.	
		•	•		•	•

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

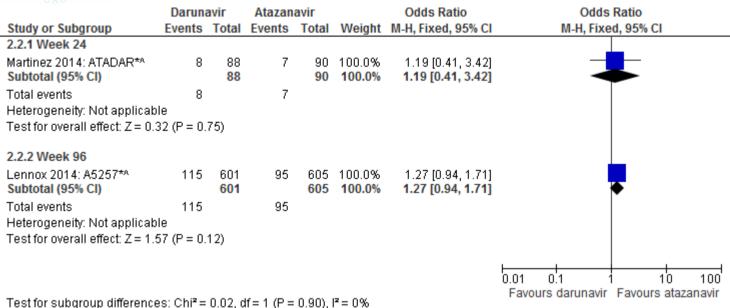




Aberg 2012 and Lennox 2014 did not report response by baseline load < or > 100,000 copies/mL.

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

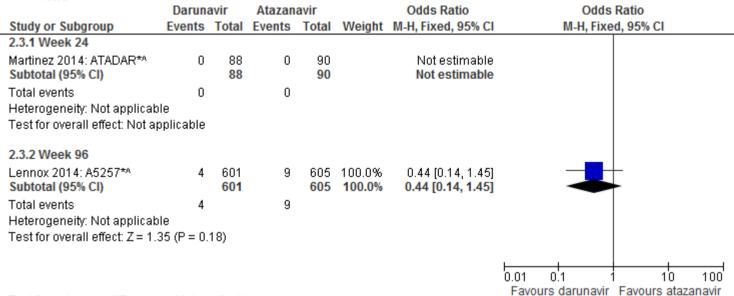




Martinez and Lennox 2014 did not report failure by baseline load < or > 100,000 copies/mL.

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

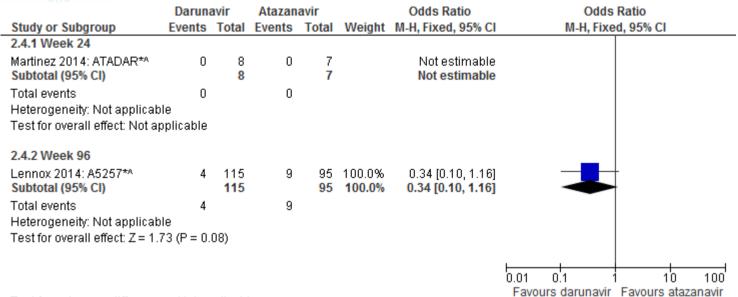




Test for subgroup differences: Not applicable

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





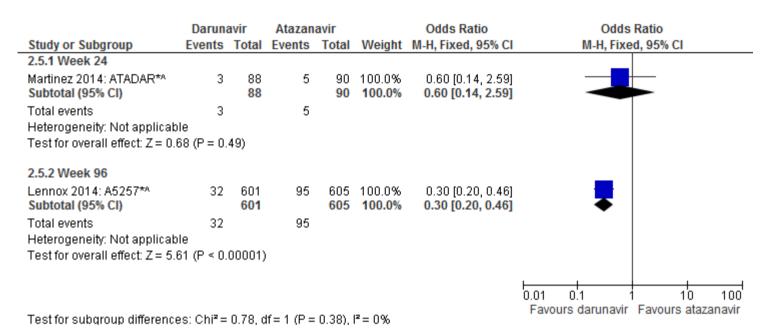
Test for subgroup differences: Not applicable

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.

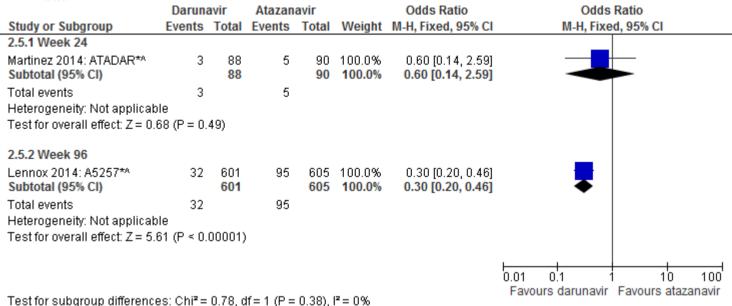


Forest plot of comparison: 2 Darunavir/ritonavir + tenofovir/emtricitabine versus atazanavir + tenofovir/emtricitabine, outcome: 2.5 Discontinued due to adverse events.



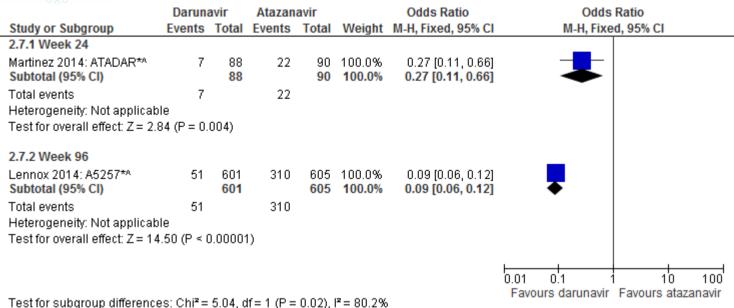
Forest plot of comparison: 2 Darunavir/ritonavir + tenofovir/emtricitabine versus atazanavir + tenofovir/emtricitabine, outcome: 2.6 Grade 3-4 adverse events (clinical).





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.

	Darun	avir	Atazan	avir		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2.8.1 Week 96							
Lennox 2014: A5257** Subtotal (95% CI)	14	601 601	12	605 605	100.0% 100.0%	1.18 [0.54, 2.57] 1.18 [0.54, 2.57]	-
Total events Heterogeneity: Not appli Test for overall effect: Z=		= 0.68)	12				
							0.01 0.1 1 10 100 Favours darunavir Favours atazanavir

Test for subgroup differences: Not applicable



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

	Darun	avir	Atazan	avir		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2.9.1 Week 96							
Lennox 2014: A5257*^ Subtotal (95% CI)	6	601 601	11	605 605	100.0% 100.0%	0.54 [0.20, 1.48] 0.54 [0.20, 1.48]	
Total events Heterogeneity: Not appli Test for overall effect: Z=		= 0.23)	11				
							0.01 0.1 1 10 100 Favours darunavir Favours atazanavir

Test for subgroup differences: Not applicable

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



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

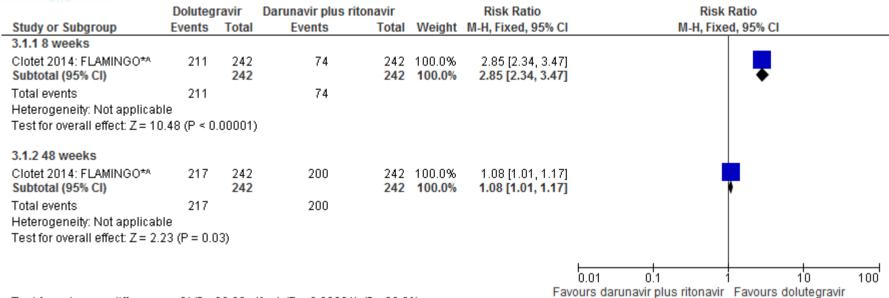
Reference	Study type and	No. pts	Patient	Intervention	Comparison	Follow-	Outcome measures	Funding
	methodological quality		characteristics			up		
Bonaventura	RCT: phase 3b, randomised,	488	Eligible patients (aged	Dolutegravir 50	Darunavir 800 mg	96	The pre-specified primary	ViiV
Clotet, et al,	open-label,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



8	, ·			1		
	evaluable patients per	past 5 years) or			set as 12%	
	group to have 90% power	ongoing malignancy,				
	with a 12% non-inferiority	or treatment with an				
	margin and a one-sided	HIV-1 vaccine within				
	2.5% significance level	90 days of screening				
		or with any				
	Intention to treat analysis:	immunomodulator				
	The authors did the	within 28 days.				
	analyses on the modified					
	intention-to-treat exposed	Patients could receive				
	or modified safety	abacavir–lamivudine				
	populations, which	only after screening				
	consisted of all patients	negative for the				
	randomly assigned to	HLA-B57*01 allele.				
	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					
		l				

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.



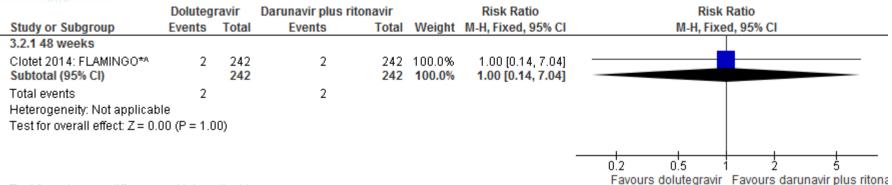


Test for subgroup differences: $Chi^2 = 82.38$, df = 1 (P < 0.00001), $I^2 = 98.8\%$

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.





Test for subgroup differences: Not applicable

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).

	Doluteg	ravir	Darunavir plus i	ritonavir		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
3.3.1 48 weeks							
Clotet 2014: FLAMINGO** Subtotal (95% CI)	0	242 242	0	242 242		Not estimable Not estimable	
Total events Heterogeneity: Not applicat Test for overall effect: Not a			0				
Tarkés a changa diécara							0.2 0.5 1 2 5 Favours dolutegravir Favours darunavir plus riton

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: 3.4 Resistance (% of those with virological failure).

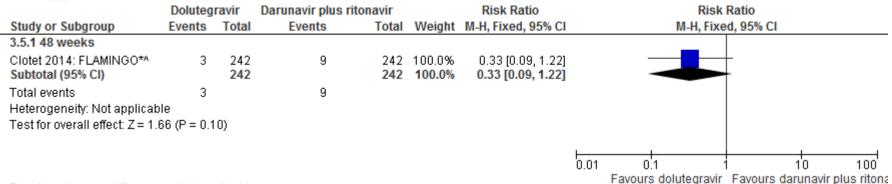
	Doluteg	ravir	Darunavir plus r	itonavir		Risk Ratio		Risk	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI
3.4.1 48 weeks									
Clotet 2014: FLAMINGO** Subtotal (95% CI)	0	2 2	0	2 2		Not estimable Not estimable			
Total events Heterogeneity: Not applicat Test for overall effect: Not a			0						
- 16 1 10							0.2 Favour	0.5 s dolutegravir	1 2 5 Favours darunavir plus rito

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.





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).

	Doluteg	ravir	Darunavir plus	ritonavir		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
3.6.1 48 weeks							
Clotet 2014: FLAMINGO** Subtotal (95% CI)	26	242 242	13	242 242	100.0% 100.0%	2.00 [1.05, 3.80] 2.00 [1.05, 3.80]	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 2.		03)	13				
							0.2 0.5 1 2 5
T16							Favours dolutegravir Favours darun

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.

	Doluteg	ravir	Darunavir plus r	itonavir		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI	
3.7.1 48 weeks										
Clotet 2014: FLAMINGO*^ Subtotal (95% CI)	4	242 242	0	242 242		9.00 [0.49, 166.26] 9.00 [0.49, 166.26]				
Total events Heterogeneity: Not applicab Test for overall effect: Z = 1.		14)	0							
							0.005 Fav	0.1	1 10 Favours daruna	200 vir plus ritona

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.

	Doluteg	ravir	Darunavir plus	ritonavir		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
3.8.1 48 weeks							_
Clotet 2014: FLAMINGO*A Subtotal (95% CI)	0	242 242	1	242 242	100.0% 100.0%	0.33 [0.01, 8.14] 0.33 [0.01, 8.14]	
Total events Heterogeneity: Not applicab Test for overall effect: Z = 0.0		50)	1				
T-16							0.005 0.1 1 10 200 Favours dolutegravir Favours darunavir plus ritona

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)

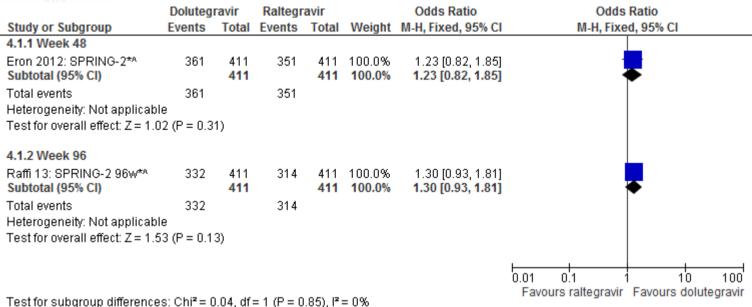
Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparis	Follow-	Outcome	Funding
					on	up	measures	
Eron Jr, J et al for	Design: phase 3, randomised, double-blind,	827	Inclusion: Eligible	Dolutegravir 50	Raltegravi	96	The pre-	ViiV
the <mark>SPRING-2</mark>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



000				
on behalf of the	per mL at week 48 was greater than -10%.	after exclusion of the	and 77	outcomes. The
extended SPRING-2	With an assumed 75% response rate in the	HLA-B*5701 allele.	had	authors used
Study Group.	raltegravir group, the authors needed to		baseline	EQ-5D
Once-daily	enrol 394 evaluable patients per group to		>100,000	(EuroQol,
dolutegravir versus	have 90% power with a 10% non-inferiority		copies/mL	Rotterdam,
twice-daily	margin, and a one-sided 2.5% significance		and	Netherlands), a
raltegravir in	level. The study was not fully powered for		received	generic, non-
antiretroviral-naive	secondary or subgroup analyses.		TDF/FTC	disease-specific,
adults with HIV-1				preference-
infection (SPRING-2				based utility
study): 96 week	Intention to treat analysis: The authors based			measure that
results from a	their efficacy and safety analyses on the			includes a
randomised,	intent-to-treat exposed or safety			descriptive
double-blind, non-	populations, which consisted of all patients			system and a
inferiority trial.	randomly assigned to treatment groups who			visual analogue
Lancet Infect Dis	received at least one dose of study drug.			scale, to
2013; 13: 927–35				measure health
	Drop out: 24 protocol deviation; 11 lost to			outcome at
	follow up; 11 withdrew consent (total 46/822			baseline and
	[5.6%])			weeks 24, 48,
				and 96.
	Setting: 100 sites in the USA, Canada,			
	Europe, and Australia			

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.

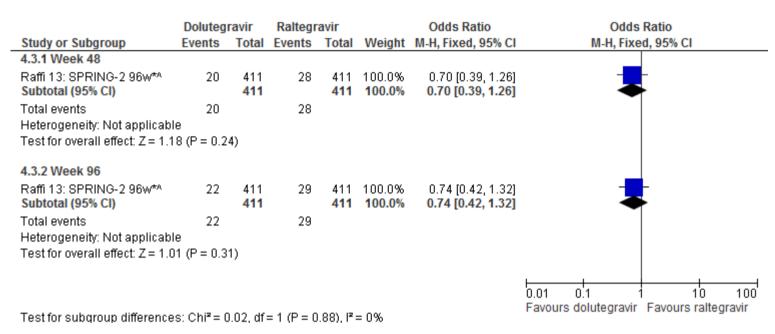


	Dolutegravi	_	avir		Odds Ratio	Odds	Ratio			
Study or Subgroup			Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	d, 95% CI			
4.2.1 Week 48; <100,000 copies/mL at baseline										
Eron 2012: SPRING-2** Subtotal (95% CI)		297 264 2 97		100.0% 100.0%	1.05 [0.62, 1.78] 1.05 [0.62, 1.78]	-				
Total events	267	264								
Heterogeneity: Not applicable										
Test for overall effect: Z = 0.1	16 (P = 0.87)									
4.2.2 Week 48; >100,000 copies/mL at baseline										
Eron 2012: SPRING-2*A	94 1	14 87		100.0%	1.57 [0.83, 2.97]	+	_			
Subtotal (95% CI)	1	114	116	100.0%	1.57 [0.83, 2.97]	+	•			
Total events	94	87								
Heterogeneity: Not applicab										
Test for overall effect: $Z = 1.3$	37 (P = 0.17)									
4.2.3 Week 96; <100,000 copies/mL at baseline										
	-		205	400.000	4 04 10 00 4 501		L			
Raffi 13: SPRING-2 96w*^ Subtotal (95% CI)		297 241 2 97		100.0% 100.0%	1.01 [0.66, 1.53] 1.01 [0.66, 1.53]	•				
Total events	243	241								
Heterogeneity: Not applicab										
Test for overall effect: $Z = 0.0$	04 (P = 0.97)									
4.2.4 Week 96; >100,000 co	ppies/mL at b	aseline					_			
Raffi 13: SPRING-2 96w*^	89 1	14 73	–	100.0%	2.10 [1.17, 3.75]		-			
Subtotal (95% CI)	1	114	116	100.0%	2.10 [1.17, 3.75]		•			
Total events	89	73								
Heterogeneity: Not applicab										
Test for overall effect: Z = 2.49 (P = 0.01)										
						0.01 0.1 1	10 100			
Tact for cubarous difference	o: Chi3 = 4 06	df = 2 /P = 0	171 12	- 20 6%		Favours raltegravir	Favours dolutegravir			

Test for subgroup differences: $Chi^2 = 4.96$, df = 3 (P = 0.17), $I^2 = 39.5\%$



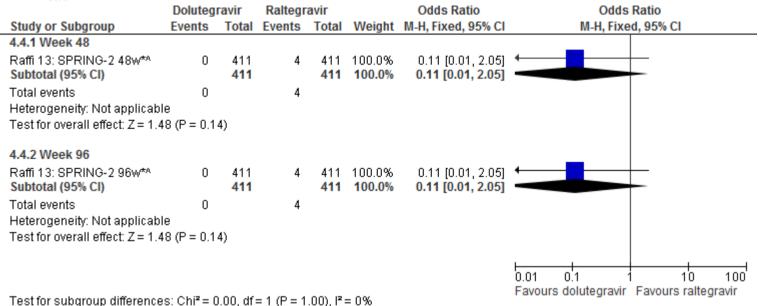
Forest plot of comparison: 4 Dolutegravir versus raltegravir, with investigator-selected NRTIs (TDF/FTC or ABC/3TC), outcome: 4.3 Virological failure.



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

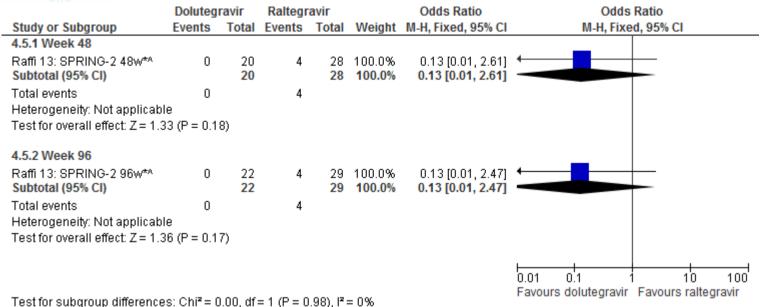
Forest plot of comparison: 4 Dolutegravir versus raltegravir, with investigator-selected NRTIs (TDF/FTC or ABC/3TC), outcome: 4.4 Resistance (% total population).





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).

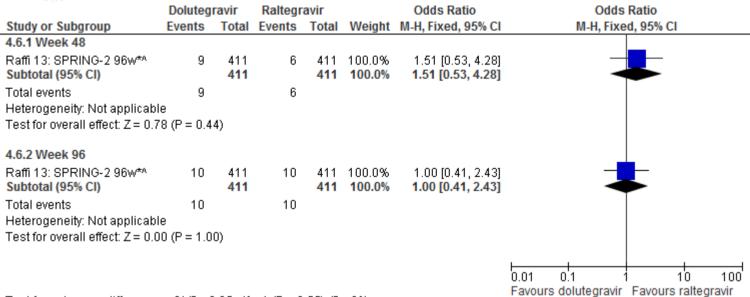




At 48 weeks, no patient with protocol-defined virological failure who received dolutegravir had treatment-emergent integrase or NRTI resistance. Notably, one patient in the raltegravir group with baseline plasma HIV-1 RNA of more than 3 million copies per mL developed both integrase-resistant and NRTI-resistant 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.





Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.55), I² = 0%

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.

	Doluteg	ravir	Raltegi	ravir		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
4.7.1 Week 48							
Raffi 13: SPRING-2 48w*^ Subtotal (95% CI)	3	411 411	5	411 411	100.0% 100.0%	0.60 [0.14, 2.51] 0.60 [0.14, 2.51]	
Total events Heterogeneity: Not applicab Test for overall effect: Z = 0.3		8)	5				
							0.01 0.1 1 10 100 Favours dolutegravir Favours raltegravir

Test for subgroup differences: Not applicable

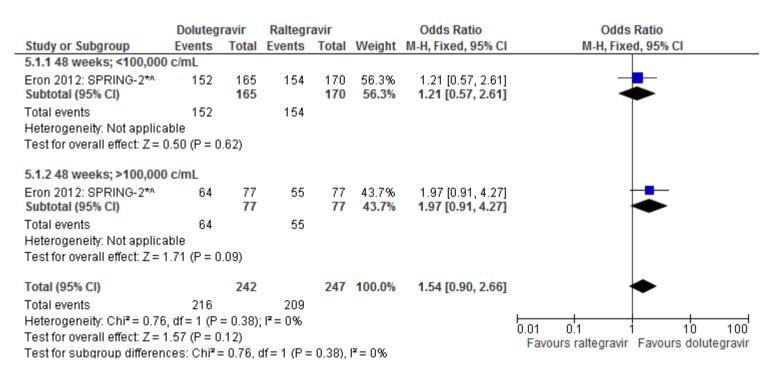
No data on Grade 3-4 adverse events (laboratory), rash, AST/ALT, CNS events or diarrhoea.



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.



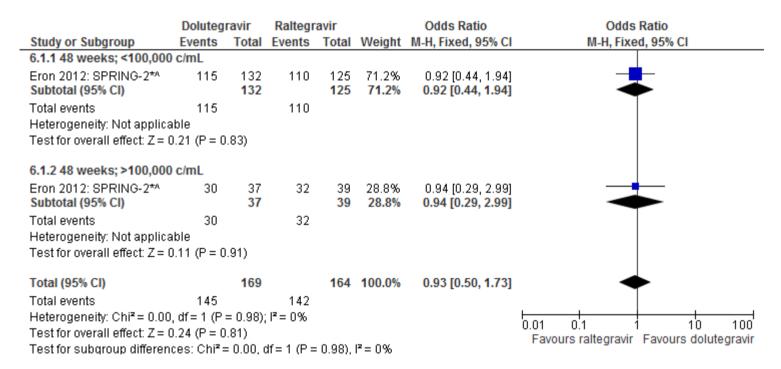
		Dolutegravir	Ralteg	ravir		Odds Ratio	Odds Ratio
S	tudy or Subgroup	Events Tot	al Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
5.	.2.1 Week 96; <100,000 co	pies/mL at ba	seline				
	affi 13: SPRING-2 96w*^ ubtotal (95% CI)	4 16 1 6		170 170		0.44 [0.13, 1.47] 0.44 [0.13, 1.47]	
Н	otal events eterogeneity: Not applicabl est for overall effect: Z = 1.3		9				
5.	.2.2 Week 96; >100,000 co	pies/mL at ba	seline				
	affi 13: SPRING-2 96w*^ ubtotal (95% CI)		'7 18 '7	77 77	65.1% 65.1%	0.38 [0.15, 0.94] 0.38 [0.15, 0.94]	.
-	otal events eterogeneity: Not applicable	8 e	18				
T	est for overall effect: Z = 2.1	0 (P = 0.04)					
T	otal (95% CI)	24	2	247	100.0%	0.40 [0.20, 0.83]	•
H	otal events eterogeneity: Chi² = 0.04, d est for overall effect: Z = 2.4 est for subgroup difference:	7 (P = 0.01)		0.84), l²:	= 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	Raltegrav	ir	Odds Ratio	Odds Ratio
Study or Subgroup	Events Total	Events T	otal Wei	ht M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
6.2.1 Week 96; <100,000 co	pies/mL at base	line			
Raffi 13: SPRING-2 96w*^ Subtotal (95% CI)	6 132 132	_	125 53.0 125 53.		
Total events	6	8			
Heterogeneity: Not applicable	e				
Test for overall effect: Z = 0.6	5 (P = 0.51)				
6.2.2 Week 96; >100,000 co	pies/mL at base	line			
Raffi 13: SPRING-2 96w*^ Subtotal (95% CI)	4 37 37	8	39 47.0 39 47.		
Total events	4	8			
Heterogeneity: Not applicable	e				
Test for overall effect: Z = 1.1	4 (P = 0.25)				
Total (95% CI)	169		164 100.	0.59 [0.26, 1.35]	•
Total events	10	16			
Heterogeneity: Chi² = 0.21, d	f = 1 (P = 0.65); P	²= 0%			0.01 0.1 1 10 100
Test for overall effect: Z = 1.2	5 (P = 0.21)				Favours dolutegravir Favours raltegravir
Test for subgroup difference:	s: Chi ^z = 0.21, df	= 1 (P = 0.6)	5), $I^2 = 0\%$		r around dolategravii i avould raitegravii



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

Reference	Study type and	No. pts	Patient characteristics	Intervention	Comparis	Follow-	Outcome	Funding
	methodological quality				on	up	measures	
Eron Jr, J et al for the	Design: double-blind,	833	Inclusion: therapy-naïve	Dolutegravir 50	TDF/FTC/	48	Proportion of	Probably
SPRING-2 & SINGLE Study Teams.	double-dummy, non-	enrolled	adults with HIV-1 RNA	mg + ABC/3TC	EFV daily	weeks	subjects with	GlaxoSmith
Dolutegravir treatment response by	inferiority phase III study		≥1000 c/mL	daily (n=414)	(n=419)		HIV-1 RNA <50	-Kline
baseline viral load and NRTI backbone							c/mL at week	
in treatment-naive HIV-infected	Randomisation: Not		Exclusion: not stated				48 (FDA	
individuals.	stated						Snapshot, ITT-	
Journal of the International AIDS							Exposed).	
Society 2012, 15 (Suppl 4): 18264	Allocation concealment:						Tolerability,	
	Not stated						safety, & viral	
							resistance	
S. Walmsley et al.	Blinding: Not stated						evaluated.	
Dolutegravir (DTG; S/GSK1349572) +								
Abacavir/Lamivudine Once Daily	Comparable groups at							
Statistically Superior to	baseline: groups similar							
Tenofovir/Emtricitabine/Efavirenz: 48-	at baseline							
Week Results - <mark>SINGLE</mark> (ING114467).								
http://www.abstractsonline.com/Plan/	Sample size calculation:							
ViewAbstract.aspx?mID=2963&sKey=e	Not stated							
1c18d5b-830f-4b4e-8671-								
35bcfb20eed5&cKey=af219b7d-2171-	Intention to treat							
46b2-91ef-	analysis: Not stated							
b8049552c9e5&mKey=%7b6B114A1D-								
85A4-4054-A83B-04D8B9B8749F%7d	Drop out: Not stated							
ICAAC 2012 Conference Abstract								
	Setting: Not stated							

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.

	Dolutegravir/abacavir/la	mivudine	tenofovir/emtricitabine	/efaviren		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
7.2.1 48 weeks: <100,0	000 c/mL						
Eron 2012: SINGLE** Subtotal (95% CI)	253	280 280	238	288 288	56.6% 56.6%	1.97 [1.19, 3.25] 1.97 [1.19, 3.25]	-
Total events Heterogeneity: Not appi	253 licable		238				
Test for overall effect: Z	= 2.65 (P = 0.008)						
7.2.2 48 weeks: >100,0	000 c/mL						
Eron 2012: SINGLE*A Subtotal (95% CI)	111	134 134	100	131 131	43.4% 43.4%	1.50 [0.82, 2.74] 1.50 [0.82, 2.74]	
Total events Heterogeneity: Not app	111 licable		100				
Test for overall effect: Z							
Total (95% CI)		414		419	100.0%	1.76 [1.20, 2.59]	•
Test for overall effect: Z	364 .47, df = 1 (P = 0.49); I^2 = 09 = 2.89 (P = 0.004) rences: Chi ² = 0.47, df = 1 (338				0.01 0.1 10 100 Favours tenofovir/emtricitabine/efaviren FavoursDolutegravir/abacavir/lamivudine



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

	Dolutegravir/abacavir/la	mivudine	tenofovir/emtricitabine	tenofovir/emtricitabine/efaviren			Odds Ratio		
Study or Subgroup	Events	Total	Events Total W			M-H, Fixed, 95% CI	d, 95% CI		
7.3.1 Week 48									
Walmsley 12: SINGLE** Subtotal (95% CI)	10	414 414	42	419 419	100.0% 100.0%	0.22 [0.11, 0.45] 0.22 [0.11, 0.45]			
Total events Heterogeneity: Not applicat Test for overall effect: Z = 4.			42						
Total (95% CI)	,	414		419	100.0%	0.22 [0.11, 0.45]	•		
Total events Heterogeneity: Not applicat Test for overall effect: Z = 4. Test for subgroup difference	.19 (P < 0.0001)		42				0.01 0.1 1 Favours dolutegravir	10 100 Favours efavirenz	



8 Efavirenz versus efavirenz-free regimens

Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparis on	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 randomi sed	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).

				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Mollan 2014: A5095*^	0.7031	0.387	61.4%	2.02 [0.95, 4.31]	
Mollan 2014: A5142*	1.0986 1	.0793	7.9%	3.00 [0.36, 24.88]	- •
Mollan 2014: A5175*^	0.7129 0	1.7915	14.7%	2.04 [0.43, 9.62]	
Mollan 2014: A5202*	1.1878	0.759	16.0%	3.28 [0.74, 14.52]	 • • • • • • • • • • • • • • • • • • •
Total (95% CI)			100.0%	2.26 [1.24, 4.09]	•
Heterogeneity: Chi² = 0.4 Test for overall effect: Z		= 0%			0.01 0.1 1 10 100 Favours efavirenz Favours efavirenz-free

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



			days of study drug dosing.					
	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)							
Paul E Sax et al for	Design: phase 3 trial (NCT01095796; GS-	707	Inclusion: adults infected	Co-formulated	Co-	192	The primary	Gilead
the GS-US-236-0102	US-236-0 <mark>102</mark>)	randomi	with HIV-1 aged at least	elvitegravir 150	formulate	weeks	endpoint was	Sciences.
study team.		sed	18 years with plasma HIV-	mg, cobicistat	d		the proportion	
Co-formulated	Randomisation: computer-generated		1 RNA concentrations of	150 mg,	efavirenz		of patients in	
elvitegravir,	allocation sequence with a block size of		5000 copies per mL or	emtricitabine	600 mg,		the intention-	
cobicistat,	four; stratified by HIV RNA concentration		more and no previous use	200 mg, and	emtricitab		to-treat	
emtricitabine, and	at screening (≤100 000 copies per mL and		of antiretroviral drugs.	tenofovir 300	ine 200		population with	
tenofovir versus co-	>100 000 copies per mL).		Participants had to have	mg (EVG/ COBI/	mg, and		viral	
formulated efavirenz,			an estimated glomerular	FTC/ TDF) once	tenofovir		suppression	
emtricitabine, and	Allocation concealment: Investigators		filtration rate of at least	daily, plus	300 mg		(HIV RNA <50	
tenofovir for initial	randomly assigned participants to one of		70 mL/min and be	matching	(EFV/FTC/		copies per mL)	
treatment of HIV-1	the treatment groups by phone or internet		susceptible to efavirenz,	placebo (n=353)	TDF), once		at week 48	
infection: a	with an interactive system (provided and		emtricitabine, and		daily, plus		according to	
randomised, double-	managed by Bracket).		tenofovir by HIV-1		matching		snapshot	
blind, phase 3 trial,			genotype (GeneSeq		placebo		analysis as	
analysis of results	Diadia a Datia da a data da ataffica a la d		assay; Monogram		(n=354)		defined by the	
after 48 weeks.	Blinding: Patients and study staff involved		Biosciences, South San				US Food and	
Lancet 2012; 379: 2439–48	in giving study treatment, assessing outcomes, and collecting and analysing		Francisco, CA, USA) at				Drug Administration	
2439-48			screening. Additional					
David A. Wohl et al	data were masked to treatment allocation.		inclusion criteria included				(FDA). Other	
for the GS-US-236-	Comparable groups at baseline: Baseline		aspartate and alanine aminotransferase				endpoints were treatment	
	characteristics were much the same in the		concentrations of no				differences by	
0102 Study Team. A Randomized,	two treatment groups		more than five times the				subgroup,	
Double-	two treatment groups		upper limit of normal;				achievement	
Blind Comparison of	Sample size calculation: The primary end		total bilirubin of no more				and	
Single-Tablet	point was assessed by treatment non-		than 25·65 μmol/L or a				maintenance of	
Regimen	inferiority of EVG/COBI/FTC/TDF compared		normal direct bilirubin,				HIV RNA	
певинен	microfity of Eval Cobilities for compared		normar direct billi ubili,			l	THE INITA	



Elvitegravir/ with Cobicistat/ Emtricitabine/ Tenofovir DF Versus Single-Tablet Regimen Efavierac/ Entricitabine/ Tenofovir DF Versus Single-Tablet Single-Tablet Regimen Efavierac/ Entricitabine/ Tenofovir DF Versus Single-Tablet Sing	300			
Emtricitabine prespecified non-inferiority margin of 12%. Single-Tablet prespecified non-inferiority margin of 12%. Single-Tablet least 95% power to establish non-inferiority margin of least 95% power to establish non-inferiority for the percentage of patients provided at least 95% power to establish non-inferiority for the percentage of patients furnitial Treatment of HIV-1 Infection: Analysis of Week 96 Results. J Acquir Immune Defic Syndr 2014; 65 (3): e118-e121. Poncol olivation (27070; 6%); at week 96, a further 12 (2%) lost to follow up; at Mandomized Double-Blind Comparison of Coformulated Elvitegravir/ Cobicistar/ Emtricitabine/ Tenofovir Disoproxil Fundation of HIV-1 Infection: Analysis of Week 96 Results. J Acquir Immune Defic Syndr 2014; 65 (3): e118-e121. Poncol olivation (1407070; 6%); at week 96, a further 12 (2%) lost to follow up; at week 96, a further 12 (2%) lost to follow up; at week 96, a further 12 (2%) lost to follow up; at week Elavirenz/ Emtricitabine/ Tenofovir Disoproxil Fundation of 180-18 (20070) and 180-18	Elvitegravir/	with	absolute neutrophil count	concentration
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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	Blind Comparison of	follow up, withdrew consent or were non-		change in HIV
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	2013; 63: 96–100			

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.



	EVG/COBI/FT	C/TDF	EFV/FTC	/TDF		Odds Ratio	Odds Ratio
Study or Subgroup	Events		Events		Weight	M-H, Fixed, 95% CI	
9.1.1 24 weeks							
Cohen 2011: Study 104*^ Subtotal (95% CI)	43	48 48	19	23 23	100.0% 100.0%	1.81 [0.44, 7.50] 1.81 [0.44, 7.50]	
Total events	43		19				
Heterogeneity: Not applicab							
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)	240	396	04.5	375	100.0%	1.37 [0.91, 2.07]	—
Total events	348 at = 1 /D = 0.60	N: IZ = 00	315				
Heterogeneity: Chi² = 0.16, Test for overall effect: Z = 1.		1),1 - 01	o				
restror overall effect. 2 = 1.	32 (1 - 0.13)						
9.1.3 Week 96							\perp
Zolopa 2013: Study 102 Subtotal (95% CI)	293	348 348	287		100.0% 100.0 %	1.21 [0.81, 1.79] 1.21 [0.81, 1.79]	
Total events	293		287				
Heterogeneity: Not applicab	ole						
Test for overall effect: $Z = 0$.	93 (P = 0.35)						
9.1.4 Week 144							
Wohl 2014: Study 102* Subtotal (95% CI)	279	348 348	265		100.0% 100.0 %	1.33 [0.93, 1.90] 1.33 [0.93, 1.90]	
Total events	279		265				
Heterogeneity: Not applicab	ole						
Test for overall effect: $Z = 1$.	55 (P = 0.12)						
							0.01 0.1 1 10 100
Toot for cubarous difference	oo: Obi z = 0.42	df = 2.71	2 - 0.04\	13 - 000			Favours EFV/FTC/TDF Favours EVG/COBI/FTC/TDF

Test for subgroup differences: $Chi^2 = 0.42$, df = 3 (P = 0.94), $I^2 = 0\%$



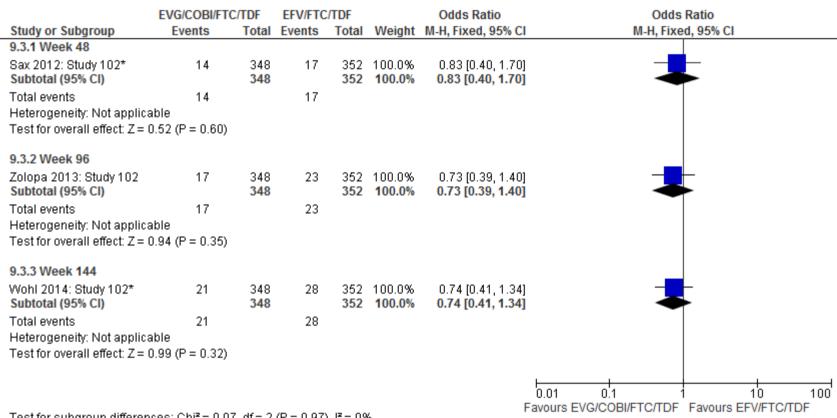
Forest plot of comparison: 9 Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate, outcome: 9.2 HIV-1 RNA less than 50 copies/ml; subgroups.

	EVG/COBI/FT(C/TDF	EFV/FTC	/TDF		Odds Ratio	Odds Ratio
Study or Subgroup	Events		Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
9.2.1 Week 96; <100,000 co	opies/mL at b	aseline					
Zolopa 2013: Study 102 Subtotal (95% CI)	197	230 230	191		100.0% 100.0%	1.41 [0.86, 2.30] 1.41 [0.86, 2.30]	
Total events	197		191				
Heterogeneity: Not applicab							
Test for overall effect: $Z = 1.3$	36 (P = 0.17)						
9.2.2 Week 96; >100,000 co	opies/mL at b	aseline					
Zolopa 2013: Study 102 Subtotal (95% CI)	96	118 118	96		100.0% 100.0%	0.91 [0.47, 1.77] 0.91 [0.47, 1.77]	*
Total events	96		96				
Heterogeneity: Not applicab	ole						
Test for overall effect: $Z = 0.5$	28 (P = 0.78)						
9.2.3 Week 144; <100,000 (copies/mL at	baselin	e				
Wohl 2014: Study 102* Subtotal (95% CI)	188	230 230	175		100.0% 100.0%	1.56 [1.00, 2.43] 1.56 [1.00, 2.43]	
Total events	188		175				
Heterogeneity: Not applicab	ole						
Test for overall effect: $Z = 1.9$	97 (P = 0.05)						
9.2.4 Week 144; >100,000	copies/mL at	baselin	e				
Wohl 2014: Study 102* Subtotal (95% CI)	91	118 118	90		100.0% 100.0%	0.97 [0.53, 1.80] 0.97 [0.53, 1.80]	*
Total events	91		90				
Heterogeneity: Not applicab	ole						
Test for overall effect: $Z = 0.0$	09 (P = 0.93)						
							0.01 0.1 1 10 100
T16							Favours EFV/FTC/TDF Favours EVG/COBI/FTC/T

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.

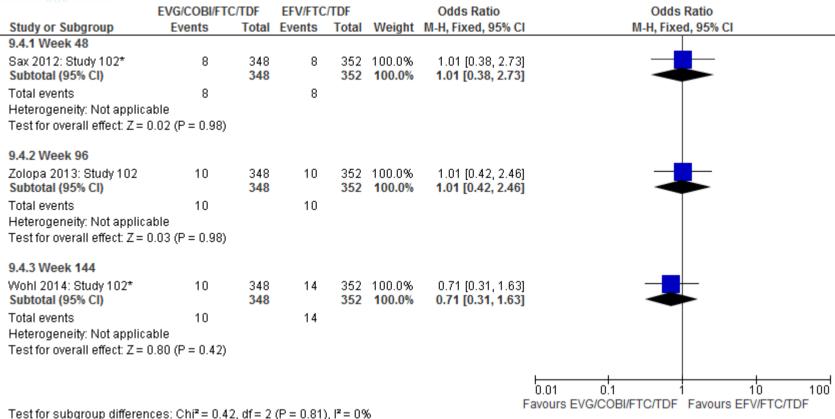


Test for subgroup differences: Chi² = 0.07, df = 2 (P = 0.97), I² = 0%

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

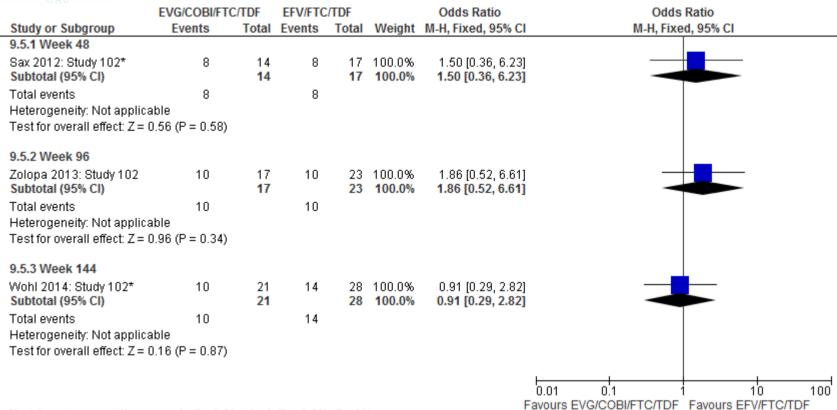
Forest plot of comparison: 9 Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate, outcome: 9.4 Resistance (% total population).





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).





Test for subgroup differences: $Chi^2 = 0.72$, df = 2 (P = 0.70), $I^2 = 0\%$

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).

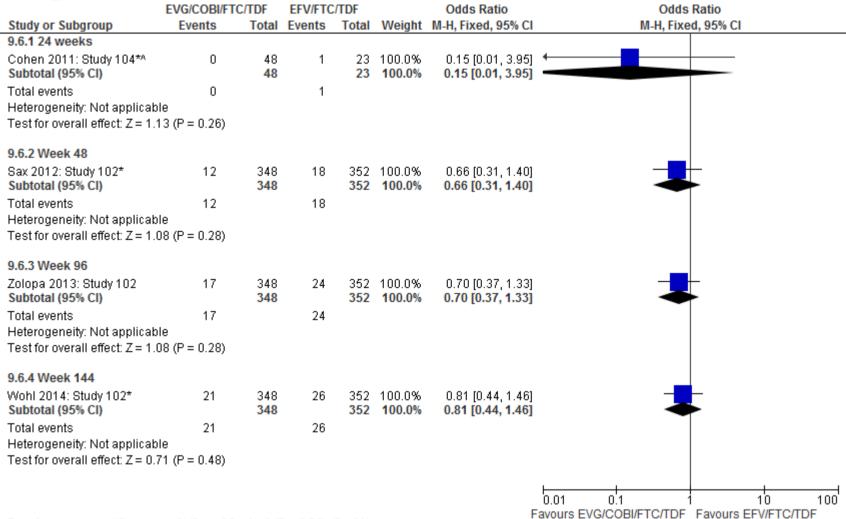


At week 96 (Zolopa 2013; Study 102): Development of resistance to 1 or more components of the regimens was infrequent through week 96. Forty patients met virologic criteria for resistance testing [EVG/COBI/FTC/TDF 17 (4.9%) vs EFV/FTC/TDF 23 (6.5%)]. Ten of 17 EVG/COBI/FTC/TDF patients had emergent resistance 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.





Test for subgroup differences: $Chi^2 = 1.05$, df = 3 (P = 0.79), $I^2 = 0\%$



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).

	EVG/COBI/FTC/TDF		EFV/FTC/TDF			Odds Ratio		Odds	Ratio	
Study or Subgroup	Events Total		Events Total		Weight	M-H, Fixed, 95% C	1	M-H, Fixe	d, 95% CI	
9.7.1 48 weeks								_		
Cohen 2011: Study 104** Subtotal (95% CI)	2	48 48	1	23 23	100.0% 100.0 %		-			
Total events Heterogeneity: Not applicabl Test for overall effect: Z = 0.0			1							
							0.01 Favours	0.1 EVG/COBI/ETC/TDE	10 Favours FEV/FTC/	100

Test for subgroup differences: Not applicable

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).

	EVG/COBI/FTC/TDF EFV/F		EFV/FTC	/TDF		Odds Ratio		Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI		
9.8.1 48 weeks											
Cohen 2011: Study 104*A Subtotal (95% CI)	0	48 48	2	23 23	100.0% 100.0%	0.09 [0.00, 1.93] 0.09 [0.00, 1.93]					
Total events Heterogeneity: Not applicab Test for overall effect: Z = 1.			2			0.00 [0.00,0]					
	01(0 0.12)						0.01	0.1	1	10	100
T16								/G/COBI/FTC/TDF	Favours I	EFV/FTC/	

Test for subgroup differences: Not applicable

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.

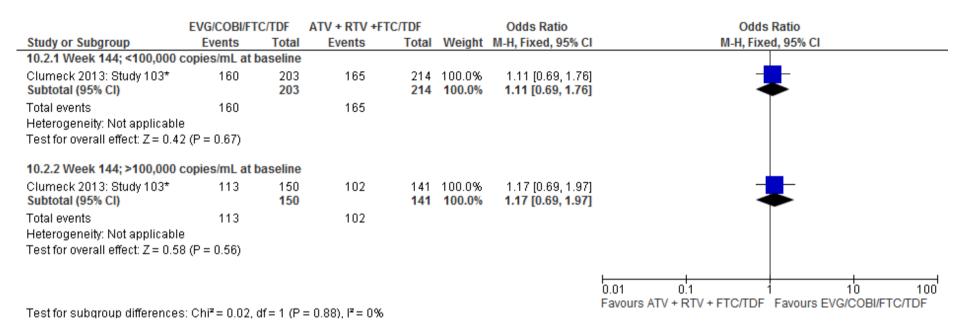
Forest plot of comparison: 10 Elvitegravir, cobicistat, emtricitabine, and tenofovir versus ritonavir-boosted atazanavir plus emtricitabine/tenofovir, outcome: 10.1 HIV-1 RNA <50 copies/mL.

	EVG/COBI/FT	C/TDF	ATV + RTV +	FTC/TDF		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
10.1.1 Week 48							
DeJesus 2012: Study 103* Subtotal (95% CI)	316	353 353	308	355 355	100.0% 100.0%	1.30 [0.82, 2.06] 1.30 [0.82, 2.06]	
Total events Heterogeneity: Not applicable	316		308				
Test for overall effect: $Z = 1.13$	(P = 0.26)						
10.1.2 Week 96							_
Rockstroh 2013: Study 103 Subtotal (95% CI)	294	353 353	292	355 355			‡
Total events Heterogeneity: Not applicable	294		292				
Test for overall effect: Z = 0.36							
10.1.3 144 weeks							
Clumeck 2013: Study 103* Subtotal (95% CI)	274	353 353	265	355 355		1.18 [0.83, 1.67] 1.18 [0.83, 1.67]	‡
Total events Heterogeneity: Not applicable	274		265				
Test for overall effect: Z = 0.93							
							0.01 0.1 1 10 100
T+6	0.00	14 0 40					Favours ATV + RTV + FTC/TDF Favours EVG/COBI/FTC/TDF

Test for subgroup differences: $Chi^2 = 0.39$, df = 2 (P = 0.82), $I^2 = 0\%$

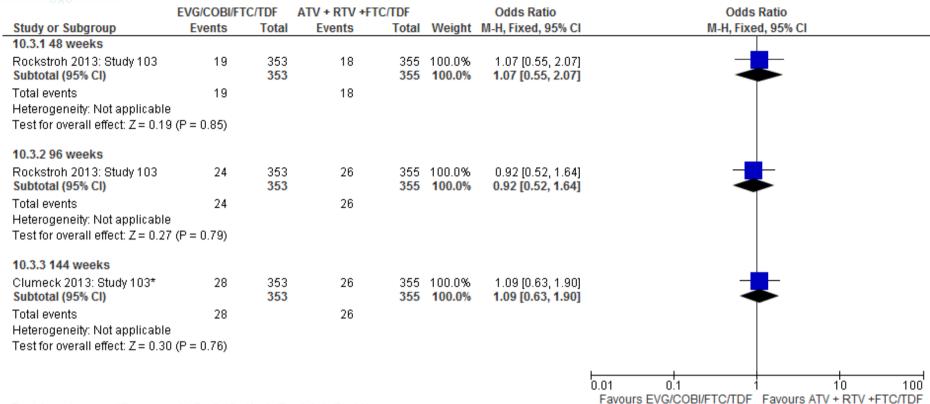


Forest plot of comparison: 10 Elvitegravir, cobicistat, emtricitabine, and tenofovir versus ritonavir-boosted atazanavir plus emtricitabine/tenofovir, outcome: 10.2 HIV-1 RNA <50 copies/mL; subgroups.



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



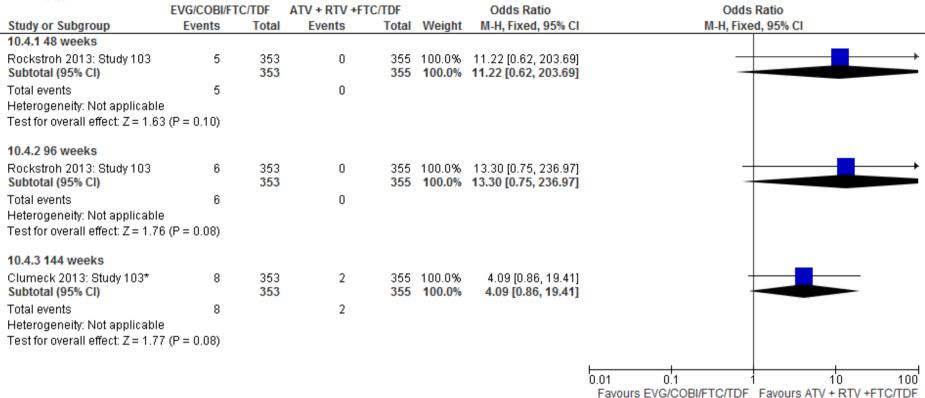


Test for subgroup differences: $Chi^2 = 0.19$, df = 2 (P = 0.91), $I^2 = 0\%$

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).

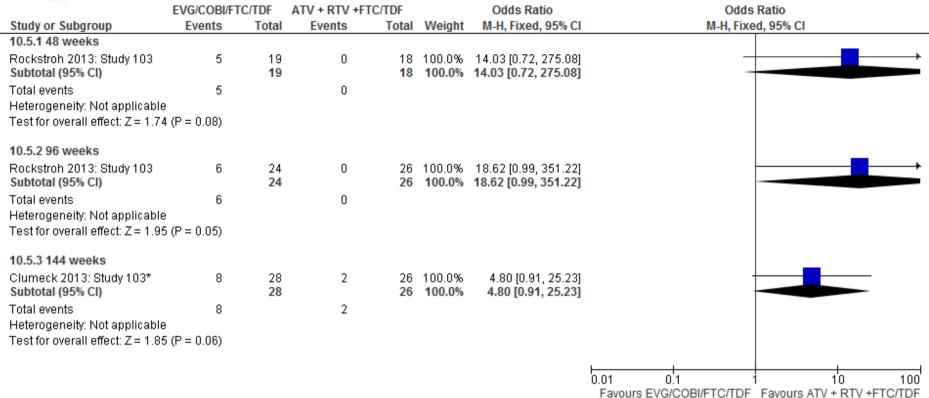




Test for subgroup differences: $Chi^2 = 0.70$, df = 2 (P = 0.70), $I^2 = 0\%$

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).





Test for subgroup differences: $Chi^2 = 0.82$, df = 2 (P = 0.67), $I^2 = 0\%$

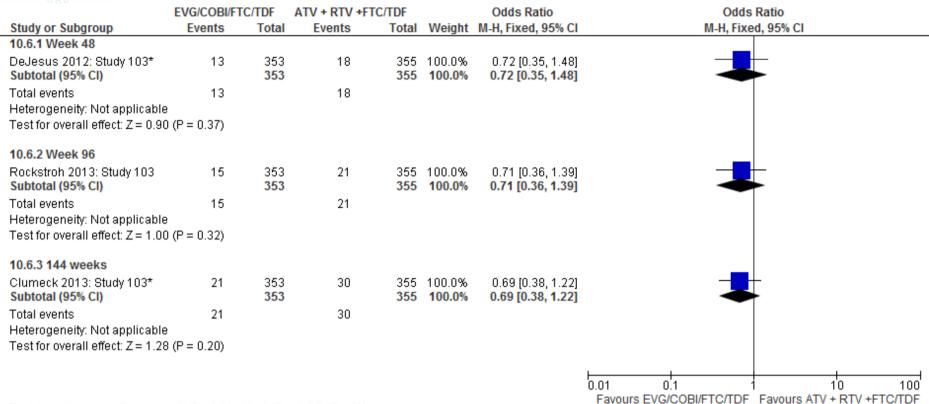
Development of resistance to one or more component of the EVG/COBI/FTC/TDF regimen was infrequent. Overall, 6 (1.7%) subjects in the EVG/COBI/FTC/TDF group failed with emergent resistance mutations vs no subjects in the ATV/RTV + FTC/TDF group. Of the 6 subjects with resistance to EVG/COBI/FTC/TDF, 5 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.

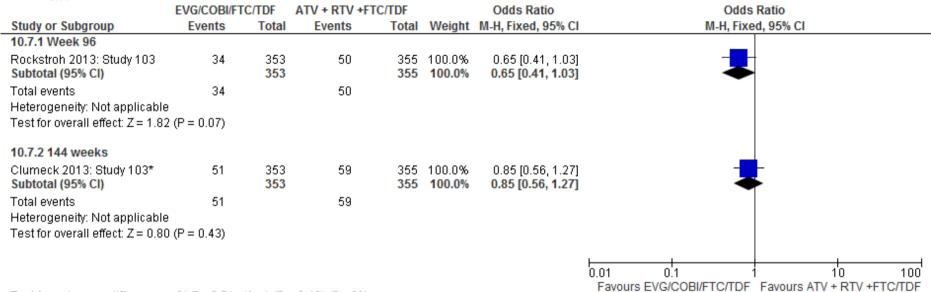




Test for subgroup differences: $Chi^2 = 0.01$, df = 2 (P = 1.00), $I^2 = 0\%$

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).





Test for subgroup differences: Chi² = 0.71, df = 1 (P = 0.40), I^2 = 0%

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.

	EVG/COBI/FTC/TDF		ATV + RTV +	FTC/TDF		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	I M-H, Fixed, 95% CI
10.8.1 Week 48							
DeJesus 2012: Study 103* Subtotal (95% CI)	47	353 353	239	355 355	100.0% 100.0%	0.07 [0.05, 0.11] 0.07 [0.05, 0.11]	· · · · · · · · · · · · · · · · · · ·
Total events Heterogeneity: Not applicable Test for overall effect: Z = 13.4		1)	239				
							0.01

Test for subgroup differences: Not applicable



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.

	Raltegr	avir	Atazanavir/rit	tonavir		Odds Ratio	Odds Ratio
Study or Subgroup	Events Total		Events Total		Weight M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
11.1.1 Week 96							
Lennox 2014: A5257** Subtotal (95% CI)	494	526 526	455	515 515	100.0% 100.0 %	2.04 [1.30, 3.18] 2.04 [1.30, 3.18]	
Total events Heterogeneity: Not appli Test for overall effect: Z =		: 0.002)	455				
							0.01 0.1 1 10 100 Favours atazanavir Favours raltegravir

Test for subgroup differences: Not applicable

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.





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

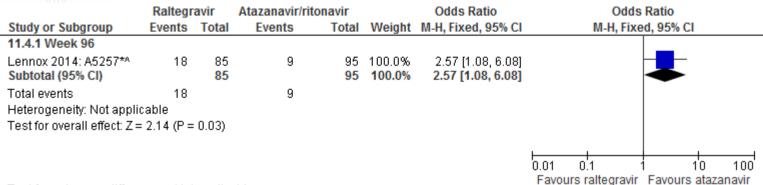
Forest plot of comparison: 11 Raltegravir vs. atazanavir/ritonavir, all with tenofovir/emtricitabine, outcome: 11.3 Resistance (% of total population).

	Raltegr	avir	Atazanavir/rit	onavir		Odds Ratio	Odds Ratio
Study or Subgroup	Events Total		Events Total		Weight M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
11.3.1 Week 96							
Lennox 2014: A5257** Subtotal (95% CI)	18	603 603	9	605 605	100.0% 100.0%	2.04 [0.91, 4.57] 2.04 [0.91, 4.57]	
Total events Heterogeneity: Not appli Test for overall effect: Z		: 0.08)	9				
							0.01 0.1 1 10 100 Favours raltegravir Favours atazanavir

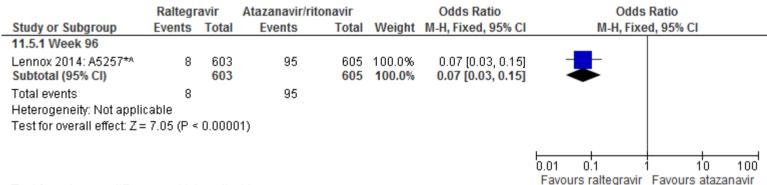
Test for subgroup differences: Not applicable

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





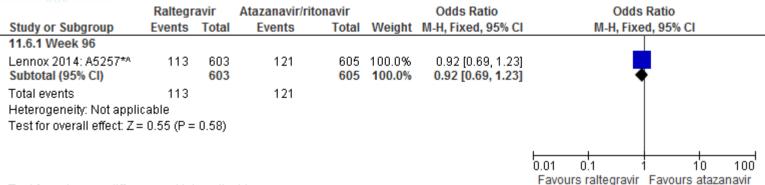
Forest plot of comparison: 11 Raltegravir vs. atazanavir/ritonavir, all with tenofovir/emtricitabine, outcome: 11.5 Discontinued due to adverse events.



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.

	Raltegr	avir	Atazanavir/rit	onavir		Odds Ratio	Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI	
11.7.1 Week 96									
Lennox 2014: A5257** Subtotal (95% CI)	41	603 603	310	605 605	100.0% 100.0%	0.07 [0.05, 0.10] 0.07 [0.05, 0.10]			
Total events Heterogeneity: Not appli Test for overall effect: Z		< 0.000	310						
							0.01 0.1 Favours raltegravir	1 10 Favours atazar	100 navir

Test for subgroup differences: Not applicable

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





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

	Raltegr	avir	Atazanavir/ri	Atazanavir/ritonavir		Odds Ratio	Odds Ratio
Study or Subgroup Events Total		Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
11.9.1 Week 96							
Lennox 2014: A5257** Subtotal (95% CI)	10	603 603	11	605 605	100.0% 100.0%	0.91 [0.38, 2.16] 0.91 [0.38, 2.16]	the state of the s
Total events Heterogeneity: Not appli Test for overall effect: Z =		: 0.83)	11				
T-16.	N	!! .					0.01 0.1 1 10 100 Favours raltegravir Favours atazanavir

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.

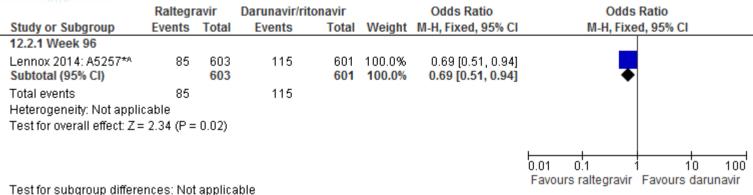
	Raltegr	avir	Darunavir/ri)arunavir/ritonavir		Odds Ratio	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI	
12.1.1 Week 96									
Lennox 2014: A5257** Subtotal (95% CI)	494	526 526	463	518 518	100.0% 100.0%	1.83 [1.16, 2.89] 1.83 [1.16, 2.89]		•	
Total events Heterogeneity: Not appli Test for overall effect: Z =		: 0.009)	463						
							0.01 0.1 Favours Darunavir	1 10 10 Favours raltegravi	

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.

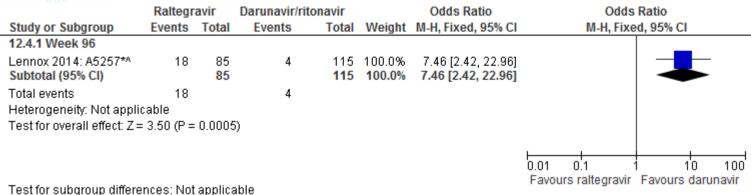
Forest plot of comparison: 12 Raltegravir vs. darunavir/ritonavir, all with tenofovir/emtricitabine, outcome: 12.3 Resistance (% total population).

	Raltegr	avir	Darunavir/rit	onavir		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
12.3.1 Week 96								
Lennox 2014: A5257** Subtotal (95% CI)	18	603 603	4	601 601	100.0% 100.0%	4.59 [1.54, 13.65] 4.59 [1.54, 13.65]		
Total events Heterogeneity: Not appli Test for overall effect: Z=		: 0.006)	4					
							0.01 0.1 1 10 Favours rattegravir Favours darung	100

Test for subgroup differences: Not applicable

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.



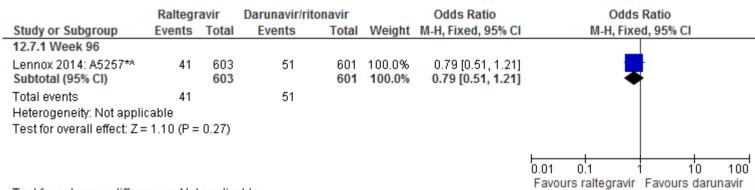
Test for subgroup differences: Not applicable

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





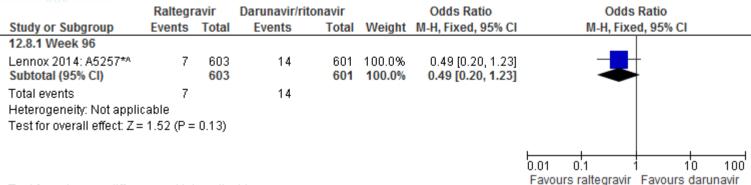
Forest plot of comparison: 12 Raltegravir vs. darunavir/ritonavir, all with tenofovir/emtricitabine, outcome: 12.7 Grade 3 or 4 laboratory adverse events.



Test for subgroup differences: Not applicable

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





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

	Raltegr	avir	Darunavir/rit	tonavir		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
12.9.1 Week 96							
Lennox 2014: A5257** Subtotal (95% CI)	10	603 603	6	601 601	100.0% 100.0%	1.67 [0.60, 4.63] 1.67 [0.60, 4.63]	-
Total events Heterogeneity: Not appli Test for overall effect: Z=		· በ 22\	6				
Test for overall ellect. 2-	- 0.55 (1* –	0.32)					0.01 0.1 1 10 100
T16			-1-1-				Favours raltegravir Favours darunavir

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



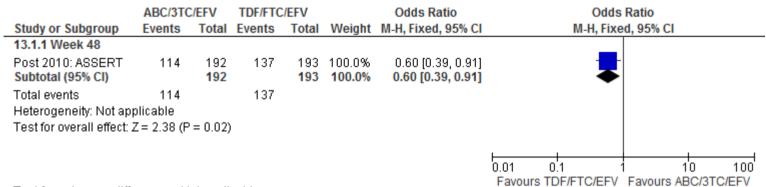
Forest plots

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):

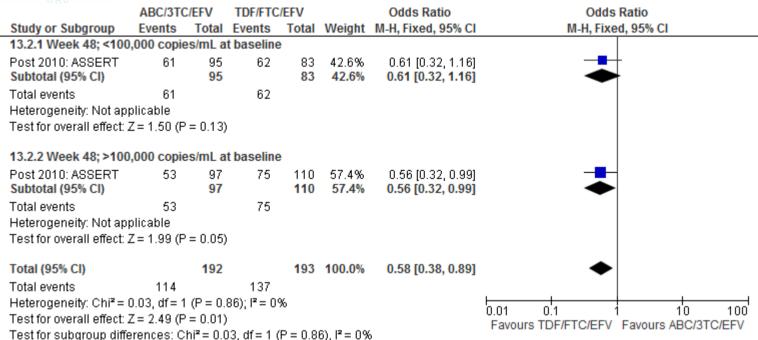
Forest plot of comparison: 13 ABC/3TC/EFV versus TDF/FTC/EFV, outcome: 13.1 HIV-1 RNA < 50 copies/mL.



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.





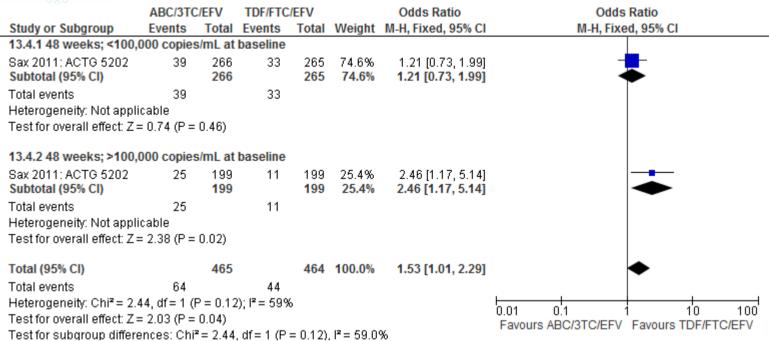
Forest plot of comparison: 13 ABC/3TC/EFV versus TDF/FTC/EFV, outcome: 13.3 Virological failure.



	ABC/3TC	/EFV	TDF/FTC	/EFV		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
13.3.1 48 weeks							
Post 2010: ASSERT	6	192	2	193	4.8%	3.08 [0.61, 15.46]	
Sax 2011: ACTG 5202 Subtotal (95% CI)	64	465 657	44	464 657	95.2% 100.0%	1.52 [1.01, 2.29] 1.60 [1.08, 2.37]	
Total events Heterogeneity: Chi² = 0. Test for overall effect: Z:			46); I² = 0%				
	,	·					0.01 0.1 1 10 100 Favours ABC/3TC/EFV Favours TDF/FTC/EFV

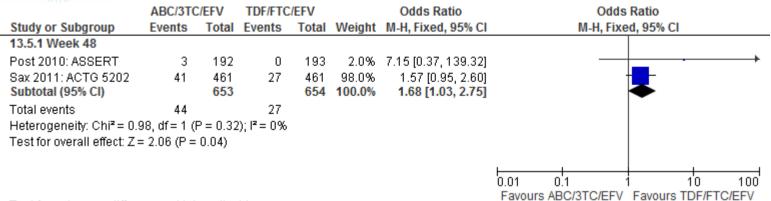
Forest plot of comparison: 13 ABC/3TC/EFV versus TDF/FTC/EFV, outcome: 13.4 Virological failure; subgroups.



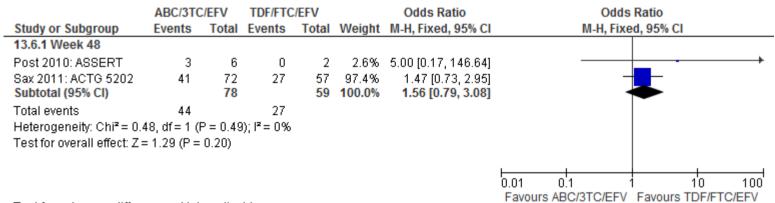


Forest plot of comparison: 13 ABC/3TC/EFV versus TDF/FTC/EFV, outcome: 13.5 Resistance (% of total population).





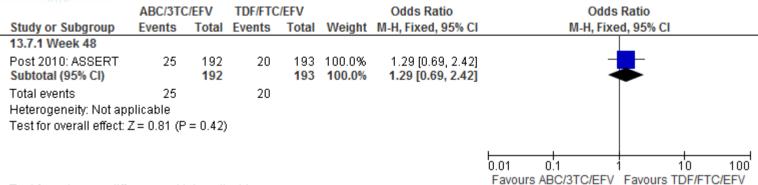
Forest plot of comparison: 13 ABC/3TC/EFV versus TDF/FTC/EFV, outcome: 13.6 Resistance (% patients with virological failure).



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.





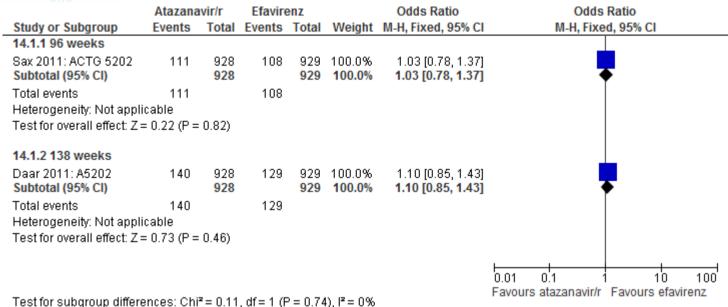
No data on other key outcomes.

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.

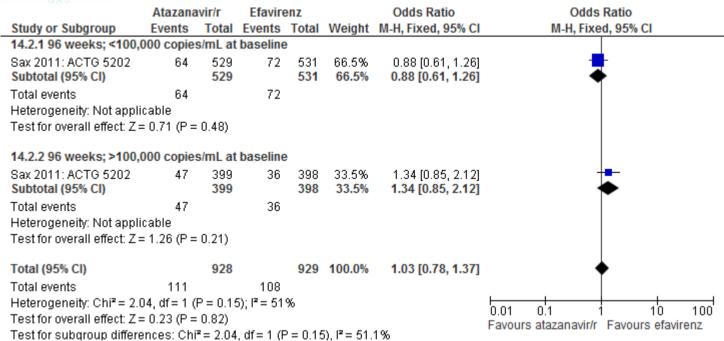
Forest plot of comparison: 14 Atazanavir-ritonavir + ABC/3TC or TDF/FTC versus efavirenz + ABC/3TC or TDF/FTC, outcome: 14.1 Virological failure.





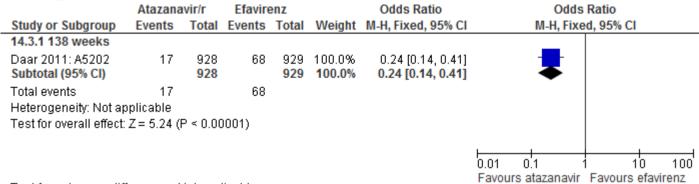
Forest plot of comparison: 14 Atazanavir-ritonavir + ABC/3TC or TDF/FTC versus efavirenz + ABC/3TC or TDF/FTC, outcome: 14.2 Virological failure; subgroups.



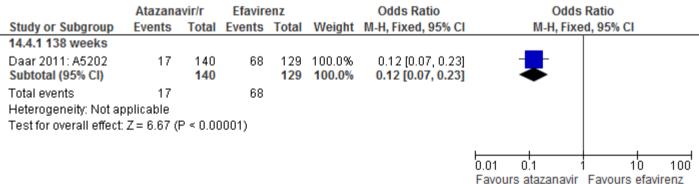


Forest plot of comparison: 14 Atazanavir-ritonavir + ABC/3TC or TDF/FTC versus efavirenz + ABC/3TC or TDF/FTC, outcome: 14.3 Resistance (% of total population).





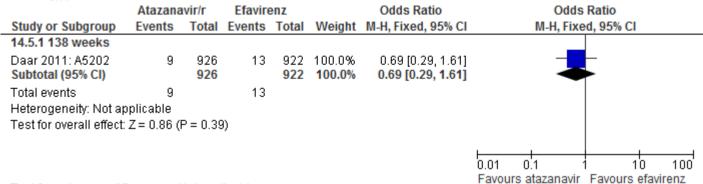
Forest plot of comparison: 14 Atazanavir-ritonavir + ABC/3TC or TDF/FTC versus efavirenz + ABC/3TC or TDF/FTC, outcome: 14.4 Resistance (% of patients with virological failure).



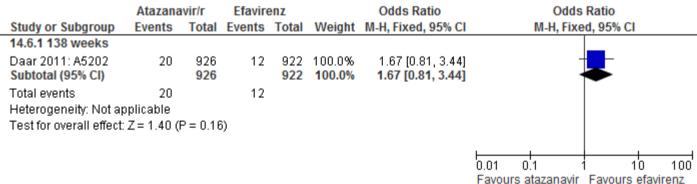
Test for subgroup differences: Not applicable

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.





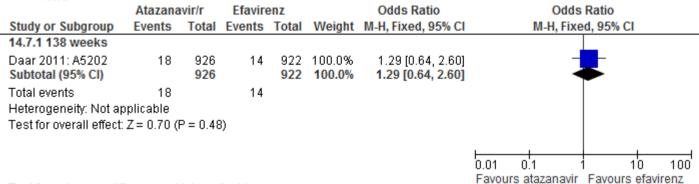
Forest plot of comparison: 14 Atazanavir-ritonavir + ABC/3TC or TDF/FTC versus efavirenz + ABC/3TC or TDF/FTC, outcome: 14.6 Grade 3 or 4 AST.



Test for subgroup differences: Not applicable

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.

	Atazana	vir/r	Efavir	enz		Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI
14.8.1 138 weeks								
Daar 2011: A5202 Subtotal (95% CI)	24	926 926	56	922 922	100.0% 100.0%	0.41 [0.25, 0.67] 0.41 [0.25, 0.67]		
Total events Heterogeneity: Not a Test for overall effect		P = 0.00	56 004)					
							0.01 0.1 Favours atazanavir	1 10 100 Favours efavirenz

Test for subgroup differences: Not applicable

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.



	Atazana	avir/r	Efavire	enz		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
14.9.1 138 weeks							
Daar 2011: A5202 Subtotal (95% CI)	13	926 926	17	922 922	100.0% 100.0%	0.76 [0.37, 1.57] 0.76 [0.37, 1.57]	
Total events Heterogeneity: Not ap Test for overall effect:	•	P = 0.46	17 6)				
							0.01 0.1 1 10 100 Favours atazanavir Favours efavirenz



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.



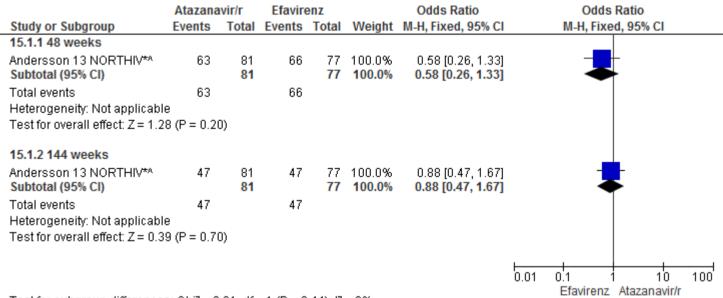
Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Length follow- up	Outcome measures	Funding
Lars-Magnus Andersson, Jan Vesterbacka, Anders Blaxhult, Leo Flamholc, Staffan Nilsson, Vidar Ormaasen, Anders Sönnerborg & Magnus Gisslén. Lopinavir/ritonavir, 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 computergenerated randomization list and was stratified by CD4 cell count (≤200 cells/µL or >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 computergenerated 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, noncompleter 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)



	and a control of the	I to a to come and
	an exclusion	between
Blinding: open-	criterion.	treatment
	David and the second	regimens based
	Baseline	on observed
Cample cize	comparability	values (and last
calculation: The	between groups:	observation
enrolment	yes	carried forward).
	Annalandaria	Analyses of
	Age: Lopinavir/r:	fasting lipids over
	37 (32 – 45);	time excluded
	Atazanavir/r:	values obtained
	39 (34 – 51);	after initiation of
	Efavirenz:	
between 2	37 (31 – 46)	serum lipid
samples with the		reduction
possibility of	Gender: female:	therapy. Median
uetecting a	36 (29%); 31	percent changes
difference in	(25%); 36 (28%)	in fasting lipids
proportions as		from baseline
cmall as h = 0.2	Severity of	were compared
(Cahan's h) with	disease: median	between
80% nower at the	CD4 cell count:	treatment
F0/ significance	150 (90 – 216);	regimens on
	170 (80 – 220);	observed cases
level.	150 (80 – 200)	(and LOCF).
ITT analysis: Yes		
111 analysis: 103		
Setting:		
Outpatients		



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

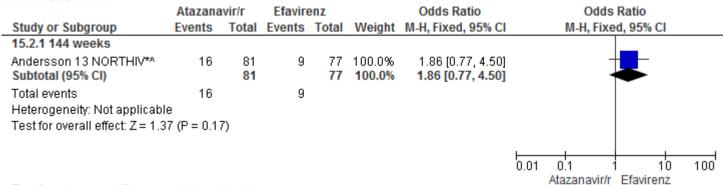


Test for subgroup differences: $Chi^2 = 0.61$, df = 1 (P = 0.44), $I^2 = 0\%$

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.





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.

	Atazana	vir/r	Efavir	enz		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
15.3.1 144 weeks							
Andersson 13 NORTHIV** Subtotal (95% CI)	5	81 81	2	77 77	100.0% 100.0%	2.47 [0.46, 13.11] 2.47 [0.46, 13.11]	
Total events Heterogeneity: Not applicabl Test for overall effect: Z = 1.0		9)	2				
Toot for outparaus differences	o: blat ann	واطومنا					0.01 0.1 1 10 100 Atazanavir/r Efavirenz

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).

	Atazana	vir/r	Efavire	enz		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
15.4.1 144 weeks							
Andersson 13 NORTHIV** Subtotal (95% CI)	16	81 81	12	77 77	100.0% 100.0%	1.33 [0.59, 3.04] 1.33 [0.59, 3.04]	The state of the s
Total events Heterogeneity: Not applicab Test for overall effect: Z = 0.6		3)	12				
							0.01 0.1 10 100 Atazanavir/r Efavirenz

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).

	Atazana	vir/r	Efavire	enz		Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI
15.5.1 144 weeks								
Andersson 13 NORTHIV** Subtotal (95% CI)	27	74 74	0	72 72	100.0% 100.0%	83.95 [5.00, 1409.39] 83.95 [5.00, 1409.39]		
Total events Heterogeneity: Not applicabl Test for overall effect: Z = 3.0		02)	0					
							0.001 0.1 Atazanavir/r	1 10 1000 Efavirenz

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).



	Atazanavir/r		Efavire	enz		Odds Ratio	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI		
15.6.1 144 weeks									
Andersson 13 NORTHIV** Subtotal (95% CI)	0	74 74	0	72 72		Not estimable Not estimable			
Total events Heterogeneity: Not applicab Test for overall effect: Not ap			0						
							0.001 0.1 1 10 100 Atazanavir/r Efavirenz		

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).

	Atazana	vir/r	Efavire	enz		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
15.7.1 144 weeks								
Andersson 13 NORTHIV** Subtotal (95% CI)	1	74 74	1	73 73	100.0% 100.0%	0.99 [0.06, 16.07] 0.99 [0.06, 16.07]		
Total events Heterogeneity: Not applicabl Test for overall effect: Z = 0.0		9)	1					
							0.001 0.1 1 10 Atazanavir/r Efavirenz	1000

Test for subgroup differences: Not applicable

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,	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 matchingimage 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	Merck



0880		 	 	
80% at we	ek 48 for both		95% CI for the	
treatment	groups and with a non-		difference in	
completer	s equals failures		response rate	
approach,	the study would have		(once-daily	
about 90%	power to show non-		raltegravir	
inferiority	of once-daily raltegravir		minus twice-	
to twice-d	aily raltegravir after		daily raltegravir)	
adjustmer	t for a small loss in		was above –	
power as a	result of the two		10%. Secondary	
planned ir	terim futility analyses		efficacy	
before the	main efficacy analysis		outcomes	
at 48 wee	cs.		included the	
			proportion of	
Intention	o treat analysis: For		patients	
calculation	of virological response		achieving	
rates, the	authors used a modified		plasma viral	
intention-	co-treat analysis that		loads of fewer	
included a	II randomised patients		than 400 copies	
receiving a	it least one dose of		per mL and	
study med	ication, and counting all		change in CD4	
non-comp	leters as failures.		cell counts from	
			baseline in each	
Drop out:	14/775 (2%) lost to		treatment	
follow up			group.	
Setting: 83	s centres (mostly			
outpatien	offices or clinics) on six			
continents	;			

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



	Raltegravir once	daily	Raltegravir twi	ce daily		Odds Ratio	Odds	s Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fix	ed, 95% CI	
16.1.1 Week 48									
Eron 2011: QDMRK*A Subtotal (95% CI)	318	382 382	343	386 386	100.0% 100.0%	0.62 [0.41, 0.94] 0.62 [0.41, 0.94]			
Total events Heterogeneity: Not appl Test for overall effect: Z			343						
							0.01 0.1 Favours ralt twice	1 10	100

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



	Raltegravir once	e daily	Raltegravir twic	e daily		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
16.2.1 Week 48; <100,	000 copies/mL at I	baseline)				
Eron 2011: QDMRK** Subtotal (95% CI)	205	230 230		234 234	41.4% 41.4%	0.72 [0.39, 1.36] 0.72 [0.39, 1.36]	•
Total events Heterogeneity: Not app	205 licable		215				
Test for overall effect: Z	= 1.01 (P = 0.31)						
16.2.2 Week 48; >100,	000 copies/mL at l	baseline					
Eron 2011: QDMRK** Subtotal (95% CI)	113	152 152		152 152	58.6% 58.6%	0.54 [0.31, 0.96] 0.54 [0.31, 0.96]	<u> </u>
Total events Heterogeneity: Not app	113 licable		128				
Test for overall effect: Z	= 2.11 (P = 0.04)						
Total (95% CI)		382		386	100.0%	0.62 [0.41, 0.94]	•
Total events Heterogeneity: Chi² = 0		0); I² = 09	343 %				0.01 0.1 1 10 10
Test for overall effect: Z	, ,		D 0.50) 13 00/				Favours ralt twice Favours ralt once
Test for subaroup differ	'ences: Uni*= 0.45	i. at = 1 (i	P = 0.50), F = 0% :				

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



	Raltegravir once	daily	Raltegravir twice	ce daily		Odds Ratio	Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI	
16.3.1 Week 48									
Eron 2011: QDMRK** Subtotal (95% CI)	53	382 382	35	388 388	100.0% 100.0%	1.62 [1.03, 2.55] 1.62 [1.03, 2.55]		•	
Total events Heterogeneity: Not appli Test for overall effect: Z			35						
							0.01 0.1 Favours ralt once	1 10	100

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



	Raltegravir once	e daily	Raltegravir twice	daily		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
16.4.1 Week 48; <100,0	00 copies/mL at	baseline					
Eron 2011: QDMRK** Subtotal (95% CI)	16	230 230	8	234 234	26.5% 26.5%	2.11 [0.89, 5.04] 2.11 [0.89, 5.04]	
Total events	16		8				
Heterogeneity: Not appli	icable						
Test for overall effect: Z:	= 1.69 (P = 0.09)						
16.4.2 Week 48; >100,0	000 copies/mL at	baseline					
Eron 2011: QDMRK*A	37	152	27	152	73.5%	1.49 [0.85, 2.60]	
Subtotal (95% CI)		152		152	73.5%	1.49 [0.85, 2.60]	
Total events	37		27				
Heterogeneity: Not appli	icable						
Test for overall effect: Z:	= 1.40 (P = 0.16)						
Total (95% CI)		382		386	100.0%	1.65 [1.04, 2.64]	
Total events	53		35				
Heterogeneity: Chi² = 0.4	44, $df = 1 (P = 0.5)$	1); $I^2 = 09$	6				0.5 0.7 1 1.5 2
Test for overall effect: Z:	= 2.11 (P = 0.03)						Favours ralt once Favours ralt twice
Test for subgroup differe	ences: Chi² = 0.44	, df = 1 (l	$P = 0.51$), $I^2 = 0\%$				ravours rait office Pavours rait (wice

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



	Raltegravir once	daily	Raltegravir twice d	aily		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
16.5.1 Week 48							
Eron 2011: QDMRK*A Subtotal (95% CI)	20	382 382	6	388 388	100.0% 100.0%	3.52 [1.40, 8.86] 3.52 [1.40, 8.86]	-
Total events Heterogeneity: Not appl	20 licable		6				
Test for overall effect: Z	= 2.67 (P = 0.008)						
T-16	Na Arroy Park						0.01 0.1 1 10 100 Favours ralt once Favours ralt twice

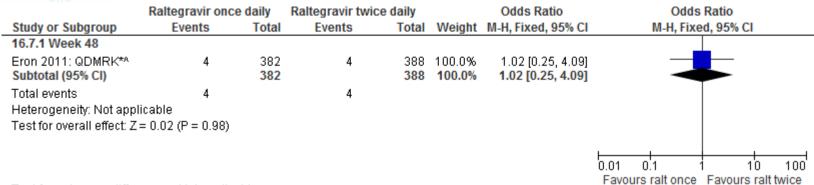
Forest plot of comparison: 16 Raltegravir once daily + tenofovir-emtricitabine versus raltegravir twice daily + tenofovir-emtricitabine, outcome: 16.6 Resistance (% patients with virological failure).

	Raltegravir once	daily	Raltegravir twice	e daily		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
16.6.1 Week 48								
Eron 2011: QDMRK*A Subtotal (95% CI)	20	53 53	6	35 35	100.0% 100.0%	2.93 [1.04, 8.29] 2.93 [1.04, 8.29]		
Total events Heterogeneity: Not appl Test for overall effect: Z			6					
							0.01 0.1 1 10 10 Favours ralt once Favours ralt twice	00 ce

Test for subgroup differences: Not applicable

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.

	Raltegravir once	daily	Raltegravir twic	e daily		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
16.8.1 Week 48								
Eron 2011: QDMRK*A Subtotal (95% CI)	26	382 382	40	388 388	100.0% 100.0%	0.64 [0.38, 1.06] 0.64 [0.38, 1.06]		
Total events Heterogeneity: Not appl Test for overall effect: Z			40					
							0.01 0.1 1 10 Favours ralt once Favours ralt tw	100 rice

Test for subgroup differences: Not applicable

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.



	Raltegravir once	daily	Raltegravir twic	e daily		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
16.9.1 Week 48							
Eron 2011: QDMRK*A Subtotal (95% CI)	11	380 380	13	386 386	100.0% 100.0%	0.86 [0.38, 1.93] 0.86 [0.38, 1.93]	#
Total events Heterogeneity: Not appl Test for overall effect: Z			13				
							0.01 0.1 1 10 100 Favours ralt once Favours ralt twice



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.



	Raltegra	vir	Efavire	nz		Odds Ratio	Odds Ratio
Study or Subgroup	_				Weight	M-H, Fixed, 95% CI	
7.1.1 Week 4							_
/ieira 2011: STARTMRK* Subtotal (95% CI)	144	279 279	33		100.0% 100.0 %	8.05 [5.22, 12.40] 8.05 [5.22, 12.40]	-
otal events	144		33				
Heterogeneity: Not applicable Test for overall effect: Z = 9.45 (P < 0.0000	1)					
7.1.2 Week 12							
/ieira 2011: STARTMRK* Subtotal (95% CI)	227	279 279	169		100.0% 100.0%	2.92 [1.99, 4.29] 2.92 [1.99, 4.29]	
otal events	227		169				
leterogeneity: Not applicable est for overall effect: Z= 5.47 (P < 0.0000	1)					
7.1.3 Week 24							
/ieira 2011: STARTMRK* Subtotal (95% CI)	244	279 279	239		100.0% 100.0 %	1.25 [0.78, 2.03] 1.25 [0.78, 2.03]	
otal events	244		239				
Heterogeneity: Not applicable Test for overall effect: Z = 0.92 ((P = 0.36)						
7.1.4 Week 40							<u></u>
/ieira 2011: STARTMRK* Subtotal (95% CI)	239	280 280	234		100.0% 100.0 %	1.17 [0.74, 1.85] 1.17 [0.74, 1.85]	7
fotal events Heterogeneity: Not applicable	239		234				
est for overall effect: Z = 0.68 ((P = 0.50)						
7.1.5 Week 48							<u>L</u>
ennox 2010: STARTMRK subtotal (95% CI)	241	280 280	230		100.0% 100.0%	1.37 [0.87, 2.16] 1.37 [0.87, 2.16]	-
otal events	241		230				
Heterogeneity: Not applicable Test for overall effect: Z = 1.36 ((P = 0.17)						
7.1.6 Week 96							
ennox 2010: STARTMRK Subtotal (95% CI)	228	281 281	223		100.0% 100.0%	1.14 [0.75, 1.72] 1.14 [0.75, 1.72]	
otal events	228		223				
Heterogeneity: Not applicable Test for overall effect: Z= 0.61 ((P = 0.54)						
7.1.7 Week 156							
Rockstroh 11: STARTMRK* Subtotal (95% CI)	212	281 281	192		100.0% 100.0%	1.44 [1.00, 2.08] 1.44 [1.00, 2.08]	•
otal events	212		192				
leterogeneity: Not applicable est for overall effect: Z= 1.94 ((P = 0.05)						
7.1.8 Week 192							
DeJesus 2012: STARTMRK* Subtotal (95% CI)	214	281 281	189		100.0% 100.0%	1.57 [1.09, 2.28] 1.57 [1.09, 2.28]	-
otal events	214		189				
Heterogeneity: Not applicable Test for overall effect: Z = 2.39 (P = 0.02)						
7.1.9 Week 240							
Rockstroh 13: STARTMRK* Subtotal (95% CI)	198	279 279	171		100.0% 100.0%	1.54 [1.08, 2.20] 1.54 [1.08, 2.20]	-
otal events	198		171			•	
Heterogeneity: Not applicable Test for overall effect: Z = 2.41 ((P = 0.02)						
							0.01 0.1 1 10 1

Test for subgroup differences: Chi² = 66.48, df = 8 (P < 0.00001), l² = 88.0%

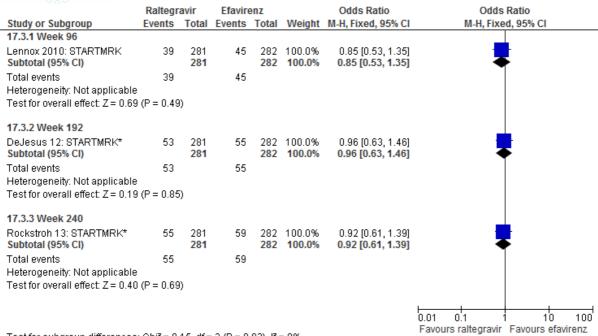


Forest plot of comparison: 17 Raltegravir + tenofovir/ emtricitabine versus efavirenz + tenofovir/ emtricitabine, outcome: 17.2 vRNA levels <50 copies/mL; subgroups.

	Raltegra	ıvir	Efavire	enz		Odds Ratio	Odds Ratio
Study or Subgroup				Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
17.2.1 Week 156; <100,000 co	•						
Rockstroh 11: STARTMRK* Subtotal (95% CI)	99	105 105	93		100.0% 100.0%	3.19 [1.22, 8.39] 3.19 [1.22, 8.39]	-
Total events	99		93				
Heterogeneity: Not applicable Test for overall effect: Z = 2.36	/D = 0.03\						
rest for overall effect. Z = 2.30	(F = 0.02)						
17.2.2 Week 156; >100,000 cd	pies/mL at	t basel	ine				
Rockstroh 11: STARTMRK* Subtotal (95% CI)	113	132 132	99		100.0% 100.0 %	1.02 [0.50, 2.07] 1.02 [0.50, 2.07]	‡
Total events	113		99				
Heterogeneity: Not applicable							
Test for overall effect: $Z = 0.06$	(P = 0.95)						
17.2.3 Week 192; <100,000 co	opies/mL a	t basel	ine				_
DeJesus 2012: STARTMRK*	98	105	86		100.0%	3.26 [1.31, 8.07]	-
Subtotal (95% CI)		105		106	100.0%	3.26 [1.31, 8.07]	-
Total events	98		86				
Heterogeneity: Not applicable Test for overall effect: Z = 2.55	/P = 0.01\						
restror overall effect. 2 = 2.33	(1 - 0.01)						
17.2.4 Week 192; >100,000 co	opies/mL a	t basel	ine				
DeJesus 2012: STARTMRK*	116	130	103		100.0%	1.05 [0.47, 2.33]	
Subtotal (95% CI)	440	130	400	116	100.0%	1.05 [0.47, 2.33]	—
Total events	116		103				
Heterogeneity: Not applicable Test for overall effect: Z = 0.11	/P = 0 91)						
7631101 0verall ellect. 2 = 0.11	(1 - 0.51)						
17.2.5 Week 240; <100,000 co	opies/mL a	t basel	ine				
Rockstroh 13: STARTMRK*	92	98	80		100.0%	4.22 [1.63, 10.92]	
Subtotal (95% CI)		98		102	100.0%	4.22 [1.63, 10.92]	-
Total events	92		80				
Heterogeneity: Not applicable Test for overall effect: Z = 2.97	(P = 0.003)						
restroi overali ellett. 2 = 2.37	(1 - 0.000)						
17.2.6 Week 240; >100,000 co	opies/mL a	t basel	ine				<u>L</u>
Rockstroh 13: STARTMRK*	106	124	91		100.0%	1.23 [0.61, 2.48]	T
Subtotal (95% CI)	4.00	124	04	110	100.0%	1.23 [0.61, 2.48]	_
Total events Heterogeneity: Not applicable	106		91				
Test for overall effect: Z = 0.58	(P = 0.56)						
	/						
							0.01 0.1 1 10 100
							Favours efavirenz Favours raltegravir
Test for subgroup differences:	$Chi^2 = 11.3$	3, df=	5(P = 0.	05), l² :	: 55.9%		

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





Test for subgroup differences: Chi² = 0.15, df = 2 (P = 0.93), I² = 0%

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

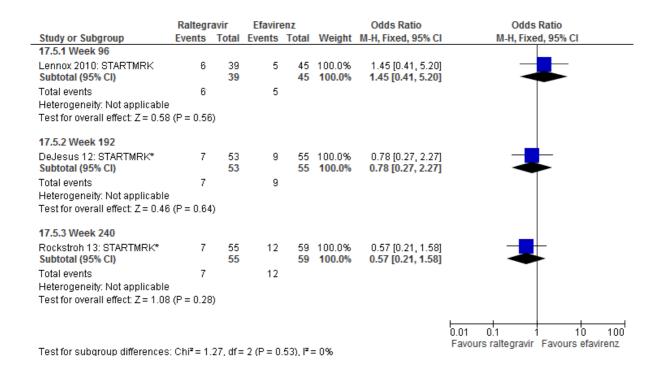
Forest plot of comparison: 17 Raltegravir + tenofovir/ emtricitabine versus efavirenz + tenofovir/ emtricitabine, outcome: 17.4 Resistance (% total population).

	Raltegra	avir	Efavire	enz		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
17.4.1 Week 96							
Lennox 2010: STARTMRK Subtotal (95% CI)	6	281 281	5	282 282	100.0% 100.0%	1.21 [0.36, 4.01] 1.21 [0.36, 4.01]	-
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.31)	5				
17.4.2 Week 192							
DeJesus 12: STARTMRK* Subtotal (95% CI)	7	281 281	9	282 282	100.0% 100.0 %	0.77 [0.28, 2.11] 0.77 [0.28, 2.11]	-
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.50)	9				
17.4.3 Week 240							
Rockstroh 13: STARTMRK* Subtotal (95% CI)	7	281 281	12		100.0% 100.0%	0.57 [0.22, 1.48] 0.57 [0.22, 1.48]	-
Total events Heterogeneity: Not applicable			12				
Test for overall effect: $Z = 1.15$	(P = 0.25))					
							0.01 0.1 1 10 10 Favours raltegravir Favours efavirenz

Test for subgroup differences: $Chi^2 = 0.91$, df = 2 (P = 0.63), $I^2 = 0\%$



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



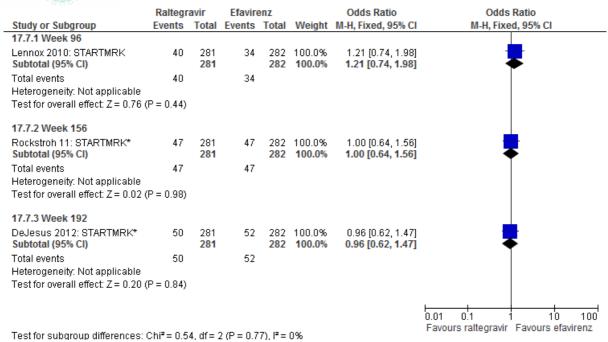
both emtricitabine and tenofovir in 1 case. In 2 additional efavirenz recipients, only emtricitabine resistance was detected.

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

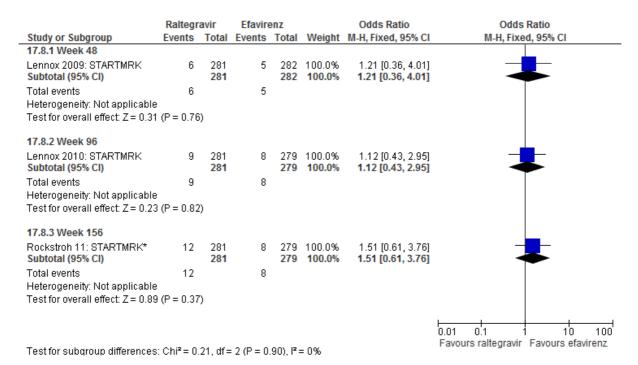
	Raltegr		Efavire			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
17.6.1 Week 48 Lennox 2009: STARTMRK	9	281	17	202	100.0%	0.52 [0.23, 1.18]	
Subtotal (95% CI)	9	281		282		0.52 [0.23, 1.18]	-
Total events	9		17				
Heterogeneity: Not applicable Test for overall effect: Z = 1.57 (P = 0.12)						
17.6.2 Week 96							
Lennox 2010: STARTMRK Subtotal (95% CI)	10	281 281	19		100.0% 100.0%	0.51 [0.23, 1.12] 0.51 [0.23, 1.12]	
Total events	10		19				
Heterogeneity: Not applicable Test for overall effect: Z = 1.68 (P = 0.09)						
17.6.3 Week 156							_
Rockstroh 11: STARTMRK* Subtotal (95% CI)	12	281 281	19		100.0% 100.0%	0.62 [0.29, 1.30] 0.62 [0.29, 1.30]	
Total events	12		19				
Heterogeneity: Not applicable Test for overall effect: Z = 1.27 (P = 0.20)						
17.6.4 Week 192							
DeJesus 2012: STARTMRK* Subtotal (95% CI)	14	281 281	26		100.0% 100.0%	0.52 [0.26, 1.01] 0.52 [0.26, 1.01]	-
Total events	14		26				
Heterogeneity: Not applicable Test for overall effect: Z = 1.93 (P = 0.05)						
17.6.5 Week 240							
Rockstroh 13: STARTMRK* Subtotal (95% CI)	14	281 281	28		100.0% 100.0%	0.48 [0.24, 0.92] 0.48 [0.24, 0.92]	.
Total events Heterogeneity: Not applicable Test for overall effect: Z = 2.19 (14 P = 0.03)		28				
							0.01 0.1 1 10 100
Test for subgroup differences: (Chi² = 0.2	8. df = 4	4 (P = 0.9	9), l²=	0%		Favours raltegravir Favours efavirenz

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



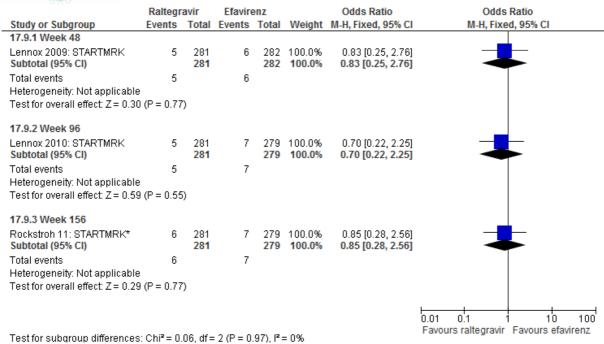


Forest plot of comparison: 17 Raltegravir + tenofovir/ emtricitabine versus efavirenz + tenofovir/ emtricitabine, outcome: 17.8 Treatment-emergent grade 3/4 abnormality in aspartate aminotransferase.



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.



	Raltegr	avir	Efavire	enz		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% C
18.1.1 Week 48							
Markowitz 2009: Prot.004 Subtotal (95% CI)	137	160 160	33	38 38	100.0% 100.0%	0.90 [0.32, 2.55] 0.90 [0.32, 2.55]	
Total events	137		33				
Heterogeneity: Not applica	ble						
Test for overall effect: $Z = 0$.19 (P = 0.	85)					
18.1.2 Week 96							
Markowitz 2009: Prot.004 Subtotal (95% CI)	133	160 160	32	38 38	100.0% 100.0%	0.92 [0.35, 2.42] 0.92 [0.35, 2.42]	
Total events	133		32				
Heterogeneity: Not applica	ble						
Test for overall effect: Z = 0	.16 (P = 0.	87)					
18.1.3 Week 240							
Gotuzzo 12: Protocol 004	110	160	24	38	100.0%	1.28 [0.61, 2.69]	-
Subtotal (95% CI)		160		38	100.0%	1.28 [0.61, 2.69]	-
Total events	110		24				
Heterogeneity: Not applica	ble						
Test for overall effect: $Z = 0$.66 (P = 0.	51)					
							<u> </u>
							0.01 0.1 1
Toot for outbarous differen	ana: Obiz-	0.40.4	f = 0 /D =	0.043	IZ — 00/		Favours efavirenz Favours

Test for subgroup differences: Chi² = 0.42, df = 2 (P = 0.81), l² = 0%

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

	Raltegr	avir	Efavire	enz		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
18.2.1 Week 240; <100,000	0 copies/i	mL at b	aseline				_L
Gotuzzo 12: Protocol 004 Subtotal (95% CI)	75	107 107	17		100.0% 100.0%	0.97 [0.36, 2.55] 0.97 [0.36, 2.55]	-
Total events Heterogeneity: Not applicat	75 ole		17				
Test for overall effect: $Z = 0$.	.07 (P = 0.	.94)					
18.2.2 Week 240; >100,000	0 copies/ı	mL at b	aseline				
Gotuzzo 12: Protocol 004 Subtotal (95% CI)	35	53 53	7	14 14	100.0% 100.0 %	1.94 [0.59, 6.40] 1.94 [0.59, 6.40]	-
Total events Heterogeneity: Not applical Test for overall effect: Z = 1.		27)	7				
Tool for overall eller. Z = 1.	.55 (1 = 0.	/					
							0.01 0.1 1 1 Favours efavirenz Favours i

Test for subgroup differences: $Chi^2 = 0.80$, df = 1 (P = 0.37), $I^2 = 0\%$

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



	Raltegr	avir	Efavire	enz		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
18.3.1 Week 96							
Markowitz 2009: Prot.004 Subtotal (95% CI)	6	160 160	2	38 38	100.0% 100.0%	0.70 [0.14, 3.62] 0.70 [0.14, 3.62]	
Total events Heterogeneity: Not applica	6 ble		2				
Test for overall effect: Z = 0	.42 (P = 0.	67)					
18.3.2 Week 240							
Gotuzzo 12: Protocol 004 Subtotal (95% CI)	10	160 160	5	38 38	100.0% 100.0%	0.44 [0.14, 1.37] 0.44 [0.14, 1.37]	
Total events Heterogeneity: Not applica Test for overall effect: Z = 1		16)	5				
restion overall effect. Z= 1	.41 (1 - 0.	10)					
							0.01 0.1 1 1
							Favours raltegravir Favours

Test for subgroup differences: $Chi^2 = 0.21$, df = 1 (P = 0.65), $I^2 = 0\%$

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

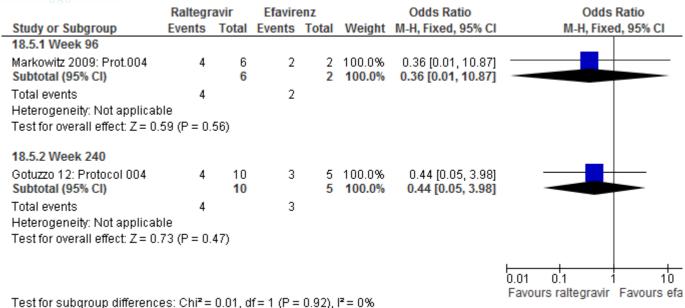
Forest plot of comparison: 18 Raltegravir + tenofovir/ lamivudine versus efavirenz + tenofovir/ lamivudine, outcome: 18.4 Resistance (% total population).

	Raltegr	avir	Efavire	enz		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
18.4.1 Week 96							
Markowitz 2009: Prot.004 Subtotal (95% CI)	4	160 160	2	38 38	100.0% 100.0%	0.46 [0.08, 2.62] 0.46 [0.08, 2.62]	
Total events Heterogeneity: Not applicab	4 le		2				
Test for overall effect: Z = 0.8	B7 (P = 0.	38)					
18.4.2 Week 240							
Gotuzzo 12: Protocol 004 Subtotal (95% CI)	4	160 160	3	38 38	100.0% 100.0%	0.30 [0.06, 1.40] 0.30 [0.06, 1.40]	
Total events Heterogeneity: Not applicab Test for overall effect: Z = 1.5		12)	3				
	01.7						0.01 0.1 1 10 Favours raltegravir Favours e

Test for subgroup differences: $Chi^2 = 0.13$, df = 1 (P = 0.71), $I^2 = 0\%$

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	Treatment Emerg	Treatment Emergent Mutations											
Group													
	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.

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

	Raltegr	avir	Efavire	enz		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
18.6.1 Week 48							
Gotuzzo 12: Protocol 004 Subtotal (95% CI)	0	160 160	0	38 38		Not estimable Not estimable	
Total events Heterogeneity: Not applicat Test for overall effect: Not a			0				
18.6.2 Week 96							
Markowitz 2009: Prot.004 Subtotal (95% CI)	2	160 160	1	38 38	100.0% 100.0%	0.47 [0.04, 5.30] 0.47 [0.04, 5.30]	
Total events Heterogeneity: Not applicat Test for overall effect: Z = 0.		54)	1				
18.6.3 Week 240							
Gotuzzo 12: Protocol 004 Subtotal (95% CI)	3	160 160	1	38 38	100.0% 100.0%		
Total events Heterogeneity: Not applicat			1				
Test for overall effect: $Z = 0$.	30 (P = 0.)	77)					
Toot for cubarous difference	oo: Obiz-	0.06 4	f_ 1 /D _	0.04	12 - 000		0.01 0.1 1 10 Favours raltegravir Favours efa

Test for subgroup differences: $Chi^2 = 0.06$, df = 1 (P = 0.81), $I^2 = 0\%$

[‡] Patient did not have sufficient virus for amplification.



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

	Raltegr	avir	Efavire	enz		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
18.7.1 Week 48							
Gotuzzo 12: Protocol 004 Subtotal (95% CI)	1	160 160	0	38 38	100.0% 100.0%	0.72 [0.03, 18.12] 0.72 [0.03, 18.12]	
Total events	1		0				
Heterogeneity: Not applicat	ole						
Test for overall effect: $Z = 0$.	.20 (P = 0.	84)					
18.7.2 Week 240							
Gotuzzo 12: Protocol 004 Subtotal (95% CI)	1	160 160	0	38 38	100.0% 100.0%	0.72 [0.03, 18.12] 0.72 [0.03, 18.12]	
Total events Heterogeneity: Not applicat	1 ole		0				
Test for overall effect: $Z = 0$.	.20 (P = 0.	84)					
							0.01 0.1 1 10 Favours raltegravir Favours efa
Test for subgroup differenc	es: Chi²=	0.00, d	lf=1 (P=	: 1.00),	$I^2 = 0\%$		

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



	Raltegr	avir	Efavire	enz		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
18.8.1 Week 48							
Gotuzzo 12: Protocol 004 Subtotal (95% CI)	9	160 160	2	38 38	100.0% 100.0%	1.07 [0.22, 5.18] 1.07 [0.22, 5.18]	-
Total events	9		2				
Heterogeneity: Not applica							
Test for overall effect: Z = 0	.09 (P = 0.	93)					
18.8.2 Week 96							L
Markowitz 2009: Prot.004 Subtotal (95% CI)	16	160 160	3	38 38	100.0% 100.0%	1.30 [0.36, 4.70] 1.30 [0.36, 4.70]	-
Total events	16		3				
Heterogeneity: Not applica							
Test for overall effect: Z = 0	.40 (P = 0.	69)					
18.8.3 Week 240							
Gotuzzo 12: Protocol 004 Subtotal (95% CI)	25	160 160	4	38 38	100.0% 100.0%	1.57 [0.51, 4.83] 1.57 [0.51, 4.83]	-
Total events	25		4				
Heterogeneity: Not applica							
Test for overall effect: Z = 0	.79 (P = 0.	43)					
							0.01 0.1 1 10
Tact for cubarous different	oo: Chi z –	0.48 8	f = 27D =	0.021	IZ 0.04		Favours raltegravir Favours efa

Test for subgroup differences: Chi 2 = 0.16, df = 2 (P = 0.92), I^2 = 0%

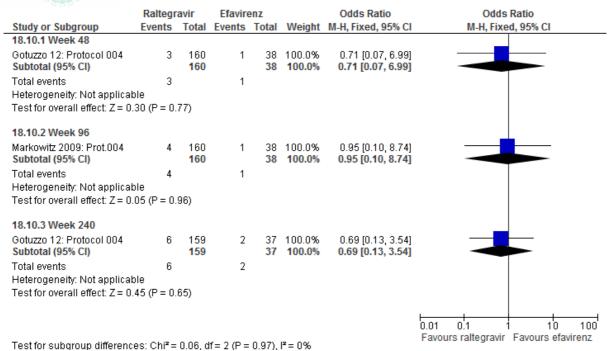
Forest plot of comparison: 18 Raltegravir + tenofovir/ lamivudine versus efavirenz + tenofovir/ lamivudine, outcome: 18.9 Drug-related clinical adverse events.

	Raltegr	avir	Efavire	enz		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
18.9.1 Week 48							
Gotuzzo 12: Protocol 004 Subtotal (95% CI)	76	160 160	27	38 38	100.0% 100.0%	0.37 [0.17, 0.79] 0.37 [0.17, 0.79]	
Total events	76		27				
Heterogeneity: Not applicab	le						
Test for overall effect: $Z = 2$.	55 (P = 0.	01)					
18.9.2 Week 240							
Gotuzzo 12: Protocol 004 Subtotal (95% CI)	88	160 160	29	38 38	100.0% 100.0%	0.38 [0.17, 0.85] 0.38 [0.17, 0.85]	
Total events	88		29				
Heterogeneity: Not applicab	le						
Test for overall effect: $Z = 2$.	35 (P = 0.	02)					
							0.01 0.1 1 10
T 1				:	17 000		Favours raltegravir Favours ef

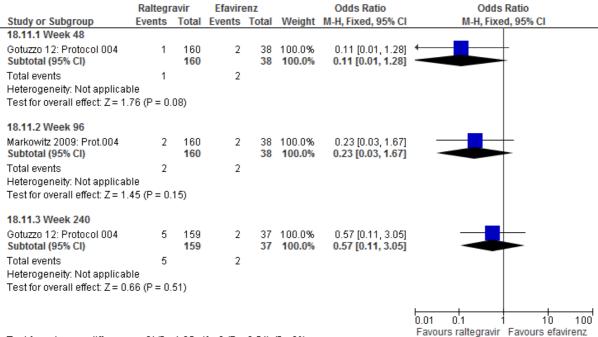
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.96), $I^2 = 0\%$

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.



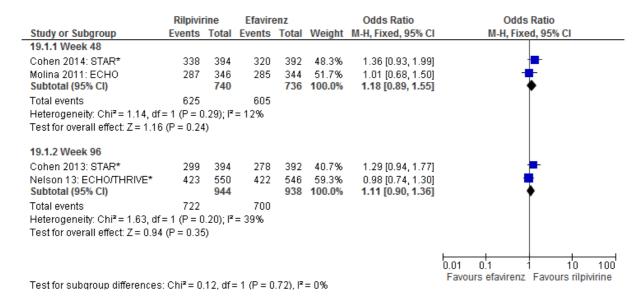
Test for subgroup differences: Chi² = 1.25, df = 2 (P = 0.54), I^2 = 0%



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

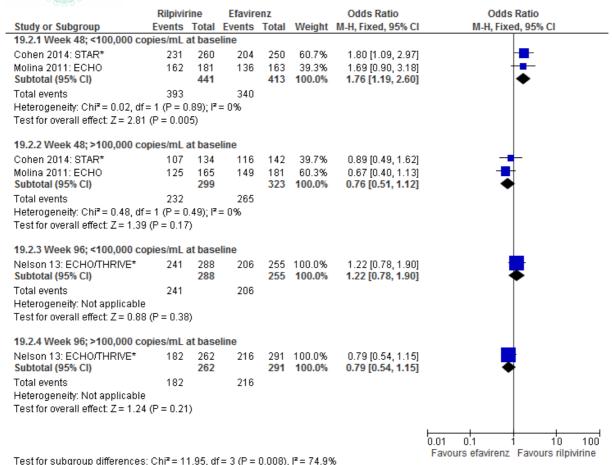
ECHO, THRIVE and STAR studies included in previous guidelines.

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

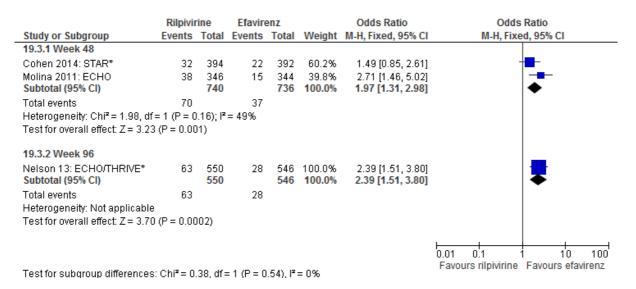


Forest plot of comparison: 19 Rilpivirine + emtricitabine/tenofovir versus efavirenz + emtricitabine/tenofovir, outcome: 19.2 HIV-1 RNA<50 copies/mL; subgroups.



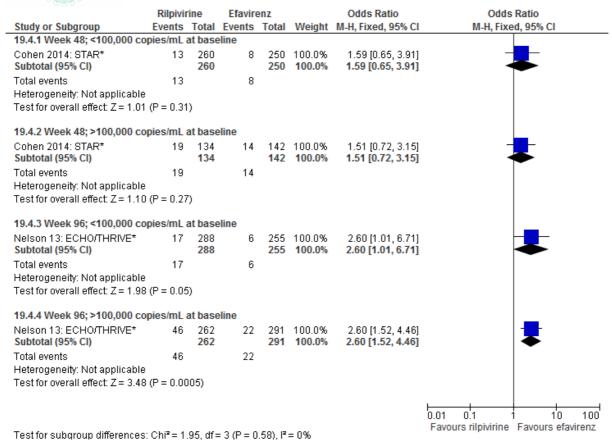


Forest plot of comparison: 19 Rilpivirine + emtricitabine/tenofovir versus efavirenz + emtricitabine/tenofovir, outcome: 19.3 Virological failure.

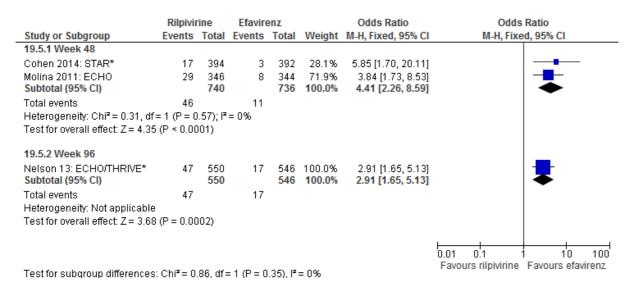


Forest plot of comparison: 19 Rilpivirine + emtricitabine/tenofovir versus efavirenz + emtricitabine/tenofovir, outcome: 19.4 Virological failure; subgroups.





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).



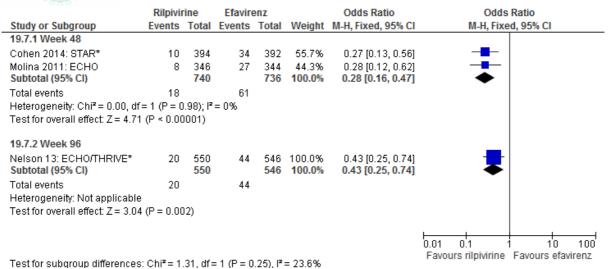
	Rilpivir	ine	Efavire	enz		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
19.6.1 Week 48							
Cohen 2014: STAR*	17	32	3	22	38.0%	7.18 [1.77, 29.16]	
Molina 2011: ECHO Subtotal (95% CI)	29	38 70	8	15 37	62.0% 100.0%	2.82 [0.80, 9.94] 4.48 [1.79, 11.17]	•
Total events	46		11				
Heterogeneity: Chi² = 0.95, df:	= 1 (P = 0	.33); l²	= 0%				
Test for overall effect: $Z = 3.21$	(P = 0.00)	11)					
19.6.2 Week 96							
Nelson 13: ECHO/THRIVE* Subtotal (95% CI)	47	63 63	17	28 28	100.0% 100.0 %	1.90 [0.74, 4.90] 1.90 [0.74, 4.90]	
Total events Heterogeneity: Not applicable	47		17				
Test for overall effect: Z = 1.33)					
							0.01 0.1 1 10 100
Test for subgroup differences	· Chi≅ – 1	62 df-	- 1 /D = 0	20) 12:	- 20 6%		Favours rilpivirine Favours efavirenz

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)].

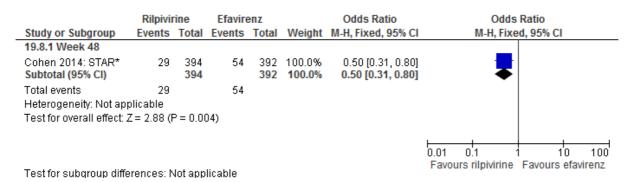
Nelson 2013: ECHO/THRIVE at week 96: Through 96 weeks, a similar proportion of subjects in both groups with virologic failure in the resistance analysis developed NNRTI mutations (55% in the RPV group and 50% in the EFV group). However, a greater proportion developed NtRTI mutations with RPV+FTC/TDF (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).

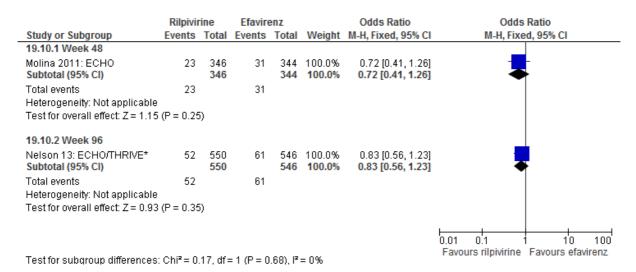


Forest plot of comparison: 19 Rilpivirine + emtricitabine/tenofovir versus efavirenz + emtricitabine/tenofovir, outcome: 19.9 Grade 3 or 4 treatment-emergent adverse event (clinical) related to study drug.

	Rilpivii	ine	Efavir	enz		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
19.9.1 Week 48							
Cohen 2014: STAR* Subtotal (95% CI)	7	394 394	19	392 392	100.0% 100.0%	0.36 [0.15, 0.85] 0.36 [0.15, 0.85]	-
Total events Heterogeneity: Not app	7 plicable		19				
Test for overall effect: 2	Z = 2.31 (F	P = 0.02	2)				
T-16		1-1	P I-1 -				0.01 0.1 1 10 100 Favours rilpivirine Favours efavirenz
Test for subgroup diffe	erences: N	lot app	licable				



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.