Appendix 3. New studies/comparisons (11 November 2021)

Methods

The search strategy is shown in Appendix A, capturing patients with HIV and comparisons of interventions. The key comparisons of interest are:

1 3rd agent comparisons

- DOL vs EFV + any 2NRTI
- DOL vs BIC + any 2NRTI
- DOL vs b/PI + any 2NRTI
- DOR vs b/PI + any 2NRTI
- DOR vs EFV + any 2NRTI
- DOL/LAM vs TDF/FTC/DOL
- DOL vs RALT + any 2NRTI

2 NRTI backbone comparison

- TDF/FTC vs TAF/FTC with any 3rd agent
- ABC/3TC vs TAF/FTC with any 3rd agent

The critical outcomes are:

- Virological suppression at 48 weeks
- Virological suppression at 96 weeks
- Virological failure at 48 weeks
- Virological failure at 96 weeks
- Failing with resistance at 48 weeks
- Failing with resistance at 96 weeks
- Adverse event (AE)-driven discontinuation
- Serious adverse events (SAE)
- Drug-related SAE
- Grade 3/4 AE
- Drug-related Grade 3/4 AE

One reviewer (JP) excluded obviously irrelevant records and a second reviewer (IR) selected the papers for inclusion for each comparison.

One reviewer (JP) extracted data and undertook a risk of bias assessment for each study using the Cochrane ROB 2.0 tool (Shown in Appendix B), and generated Forest plots and GRADE tables.

Results

3rd agent comparisons

1 DOL vs EFV + any 2 NRTI

Three trials examined this comparison. ADVANCE data were published for week 48 (Venter 2019) and week 96 results (Venter 2020). NAMSAL provided week 48 data in the NAMSAL ANRS 12313 (2019) paper. The SINGLE study data were reported for week 48 (Walmsley 2013) and week 96 and 144 (Walmsley 2015).

Table 1. Key features of the included studies

Study name/ NCT number	Citation	Inclusion criteria	Exclusions	Population (n; demographics)	Intervention	Comparator	Outcomes
NCT03122262; ADVANCE	Venter WDF, Moorhouse M, Sokhela S, Fairlie L, Mashabane N, Masenya M, Serenata C, Akpomiemie G, Qavi A, Chandiwana N, Norris S, Chersich M, Clayden P, Abrams E, Arulappan N, Vos A, McCann K, Simmons B, Hill A. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. N Engl J Med. 2019 Aug 29;381(9):803-815. doi: 10.1056/NEJMoa1902824. Epub 2019 Jul 24. PMID: 31339677.	Age ≥12 years, weight ≥40kg, viral load of ≥500 copies/mL, creatinine clearance >60 mL/min (Cockcroft–Gault formula) in patients 19 years of age or older or > 80 mL/min (modified Cockcroft–Gault formula) in those <19 years of age	>30 days of treatment with any form of ART, any ART within the past 6 months, pregnancy, or current	1053 participants with HIV infection in South Africa. The mean age was 32 years (range, 13 to 62); 14 patients were younger than 19 years of age. A total of 59% of the patients were female, more than 99% were black, and 62% were from South Africa. The mean CD4 count was 337 cells per cubic millimeter (range, 1 to 1721), and 78% of the patients had a baseline HIV-1 RNA level of less than 100,000 copies per milliliter.	Tenofovir alafenamide fumarate (TAF) plus emtricitabine (FTC) and dolutegravir (DTG) = TAF–FTC–DTG (TAF-based group) OR Tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) and dolutegravir (DTG) = TDF–FTC–	Tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) and efavirenz (EFV) = TDF–FTC–EFV (standard-care group)	The primary end point was the percentage of patients with an HIV-1 RNA level <50 copies/mL at week 48. Secondary objectives were to evaluate additional viral-load thresholds, CD4 count changes, and side-effect profile and safety, including findings on physical examination, laboratory analyses, and dual-energy x-ray absorptiometry (DXA) scans.

			treatment for tuberculosis		DTG (TDF-based group)		
	Venter, WDF; Sokhela, S; Simmons, B; Moorhouse, M; Fairlie, L; Mashabane, N; Serenata, C; Akpomiemie, G; Masenya, M; Qavi, A; Chandiwana, N; McCann, K; Norris, S; Chersich, M; Maartens, G; Lalla-Edward, S; Vos, A; Clayden, P; Abrams, E; Arulappan, N; Hill, A. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. The lancet. HIV 2020; 7(10): e666-676. DOI: 10.1016/S2352-3018(20)30241-1. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02192063/full	As above	As above	As above	As above	As above	As above
NCT02777229; New Antiretroviral and Monitoring Strategies in HIV-Infected Adults in Low-Income Countries (NAMSAL) ANRS 12313	NAMSAL ANRS 12313 Study Group, Kouanfack C, Mpoudi-Etame M, Omgba Bassega P, Eymard-Duvernay S, Leroy S, Boyer S, Peeters M, Calmy A, Delaporte E. Dolutegravir-Based or Low-Dose Efavirenz-Based Regimen for the Treatment of HIV-1. N Engl J Med. 2019 Aug 29;381(9):816-826. doi: 10.1056/NEJMoa1904340. Epub 2019 Jul 24. PMID: 31339676.	≥18 years, had not received ART, and had HIV-1 group M infection with a viral load of at least 1000 copies /mL. Women of childbearing potential had to agree to use effective	Pregnancy, breast-feeding, severe hepatic impairment, renal failure, severe psychiatric	613 participants. The median age was 37 years; 65.9% of the participants were women. The median baseline viral load was 5.3 log10 copies/mL and 66.4% of the participants had a baseline viral load of at least 100,000 copies/mL. The median CD4+ T-cell count was 281 per cubic millimeter. Of note in the NAMSAL trial, the participants were mainly women of childbearing potential, had high baseline viral loads (66.4% had a viral	Dolutegravir combined with tenofovir and lamivudine.	Low-dose efavirenz (a 400-mg dose, known as EFV400), combined with tenofovir and lamivudine.	The primary end point was the proportion of participants with a viral load of less than 50 copies per milliliter at week 48. Secondary end points included the viral load with other thresholds (a viral load of 1000 copies/mL after reinforcement of adherence) at weeks 24 and 48, as well as drug resistance; the change from baseline in the CD4+ T-cell count at weeks 24 and 48, morbidity (WHO stage), survival, adherence to

		contraceptive methods	illness, and unstable tuberculosis coinfection	load of ≥100,000 copies/mL, and 30.7% had a viral load of ≥500,000 copies/mL), and often had coexisting conditions, whereas the participants included in the SINGLE trial were predominantly men, and one third had a baseline viral load of at least 100,000 copies/mL.			treatment, safety, and patient-reported outcomes (depression, anxiety, and stress; HIV treatment symptoms, including efavirenz-related symptoms; and quality of life)
NCT01263015; SINGLE	Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutiérrez F, Hocqueloux L, Maggiolo F, Sandkovsky U, Granier C, Pappa K, Wynne B, Min S, Nichols G; SINGLE Investigators. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med. 2013 Nov 7;369(19):1807-18. doi: 10.1056/NEJMoa1215541. PMID: 24195548.	≥18 years, had HIV-1 infection, had not previously received ART, had a plasma HIV-1 RNA level of at least 1000 copies/mL without genotypic evidence of viral resistance at screening, and were negative for the HLA-B*5701 allele.	Women who were pregnant or breast-feeding, persons with moderate or severe hepatic impairment, and persons with an estimated creatinine	844 participants. The median age was 35 years; 16% of the participants were women, 24% were black, and 4% were in class C of the Centers for Disease Control and Prevention HIV classification system (defined as the presence of specific opportunistic infections). The median HIV-1 RNA level at baseline was 4.68 log10 copies/mL, and the median CD4+ T-cell count was 338 per cubic millimeter.	Dolutegravir plus abacavir–lamivudine	Efavirenz–tenofovir disoproxil fumarate (DF)-emtricitabine	The primary end point was the proportion of participants with an HIV-1 RNA level of less than 50 copies/mL at week 48. Secondary end points included the time to viral suppression, the change from baseline in CD4+ T-cell count, safety, and viral resistance.

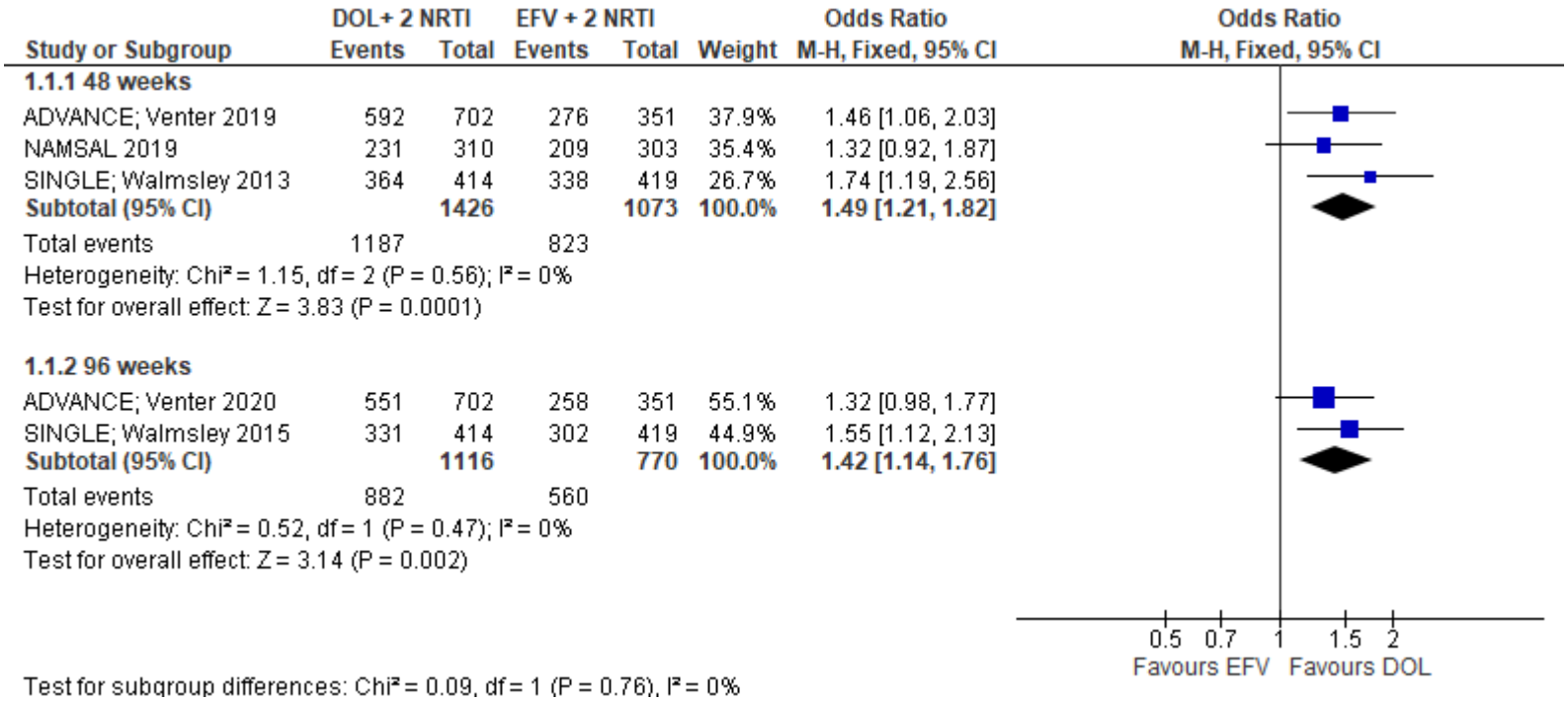
			clearance <50 mL/min				
	Walmsley S, Baumgarten A, Berenguer J, Felizarta F, Florence E, Khuong-Josses MA, Kilby JM, Lutz T, Podzamczer D, Portilla J, Roth N, Wong D, Granier C, Wynne B, Pappa K. Brief Report: Dolutegravir Plus Abacavir/Lamivudine for the Treatment of HIV-1 Infection in Antiretroviral Therapy-Naive Patients: Week 96 and Week 144 Results From the SINGLE Randomized Clinical Trial. J Acquir Immune Defic Syndr. 2015 Dec 15;70(5):515-9. doi: 10.1097/QAI.0000000000000790. Erratum in: J Acquir Immune Defic Syndr. 2016 Jan 1;71(1):e33. PMID: 26262777; PMCID: PMC4645960.	As above	As above	As above	As above	As above	As above

Table 2. Comparisons included in this section

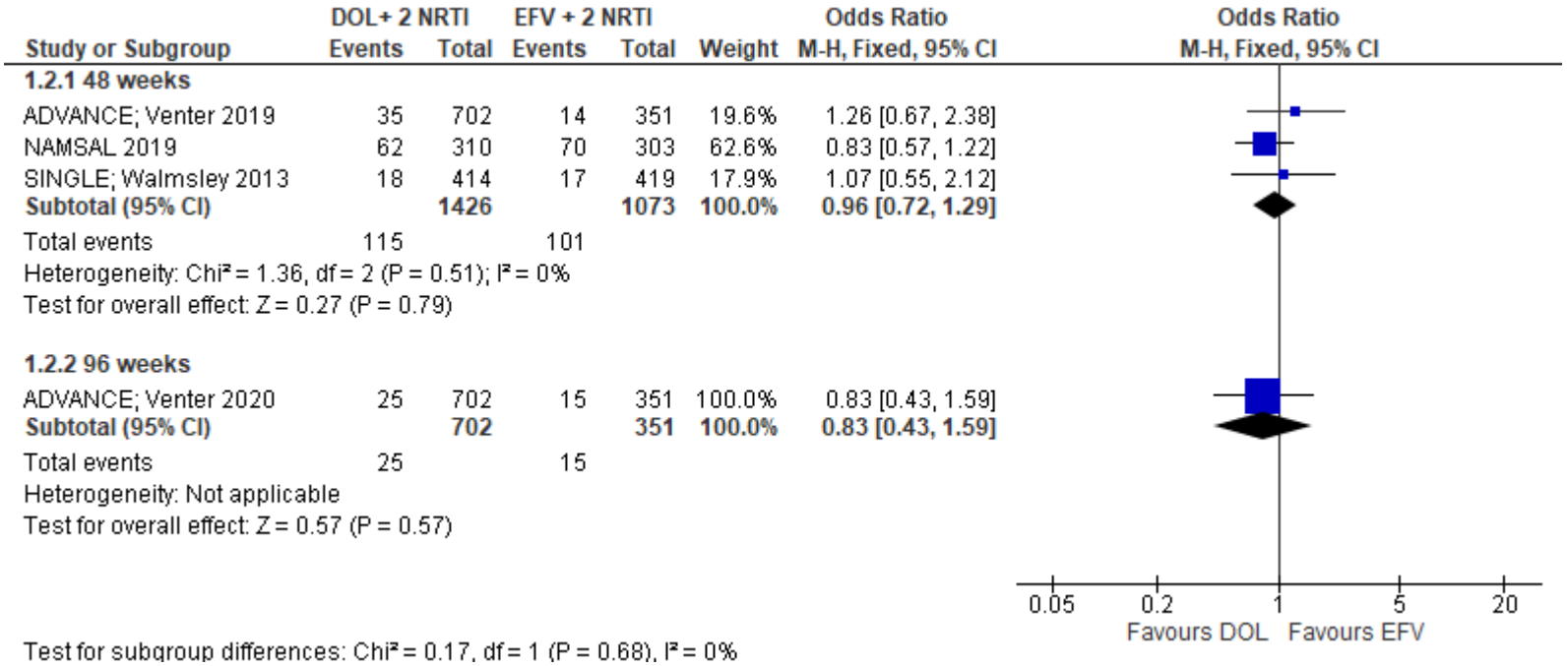
Study name/ NCT number	Intervention (Two NRTI + DOL)	Comparator (2 NRTI + EFV)
NCT03122262; ADVANCE	Tenofovir alafenamide fumarate (TAF) plus emtricitabine (FTC) and dolutegravir (DTG) = TAF–FTC–DTG (TAF-based group) OR Tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) and dolutegravir (DTG) = TDF–FTC–DTG (TDF-based group) The two groups were combined in the analyses.	Tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) and efavirenz (EFV) = TDF–FTC–EFV (standard-care group)
NCT02777229; New Antiretroviral and Monitoring Strategies in HIV-Infected Adults in Low-Income Countries (NAMSAL) ANRS 12313	Dolutegravir, tenofovir and lamivudine.	Low-dose efavirenz (a 400-mg dose, known as EFV400), tenofovir and lamivudine.
NCT01263015; SINGLE	Dolutegravir, abacavir and lamivudine	Efavirenz, tenofovir disoproxil fumarate and emtricitabine

Virological success, failure and missing data

Forest plot of comparison: 1 DOL vs EFV + any 2 NRTI, outcome: 1.1 Virological success.



Forest plot of comparison: 1 DOL vs EFV + any 2 NRTI, outcome: 1.2 Virological failure.



Of note, in the ADVANCE study, by week 48, the number of patients who had discontinued treatment or who had missing data was 41 (12%) in the TAF-based group, 39 (11%) in the TDF-based group, and 55 (16%) in the EFV group. Differences in efficacy between the groups were driven by a higher number of discontinuations in the standard-care group than in the other two groups. In the per-protocol analysis, the percentage of patients with an HIV-1 RNA level of less than 50 copies/mL was similar across the groups at week 48 (96% in the TAF-based group, 95% in the TDF-based group, and 96% in the standard-care group). At week 96, 11 (3%) of 351 participants in the TAF-based group, 14 (4%) of 351 participants in the TDF-based group, and 15 (4%) of 351 participants in the EFV group had plasma HIV-1 RNA concentrations of 50 copies per mL or higher at week 96 or discontinued due to poor efficacy. All other patients discontinued before week 96.

Similarly in the SINGLE trial, the superior responses in the DOL group at week 48 were driven primarily by a lower rate of discontinuation due to adverse events in the DTG–ABC–3TC group than in the EFV–TDF–FTC group (10 of 414 participants [2%] in the DTG–ABC–3TC group and 42 of 419 [10%] in the EFV–

TDF–FTC group). Also, at week 96, differences in the virological response rate were driven by a lower rate of discontinuations due to AEs or deaths in the dolutegravir + abacavir/ lamivudine arm than in the efavirenz/tenofovir DF/emtricitabine arm: 13/414 (3%) vs. 48/419 (11%).

Figure: 1. Success, failure and missing data at 48 weeks

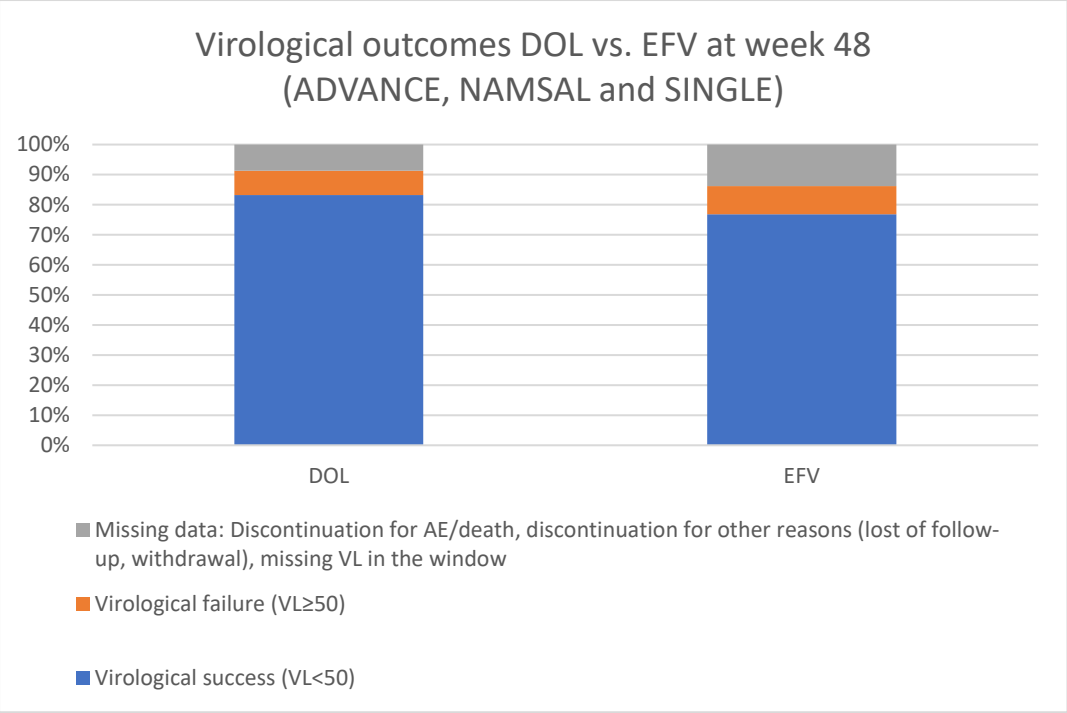
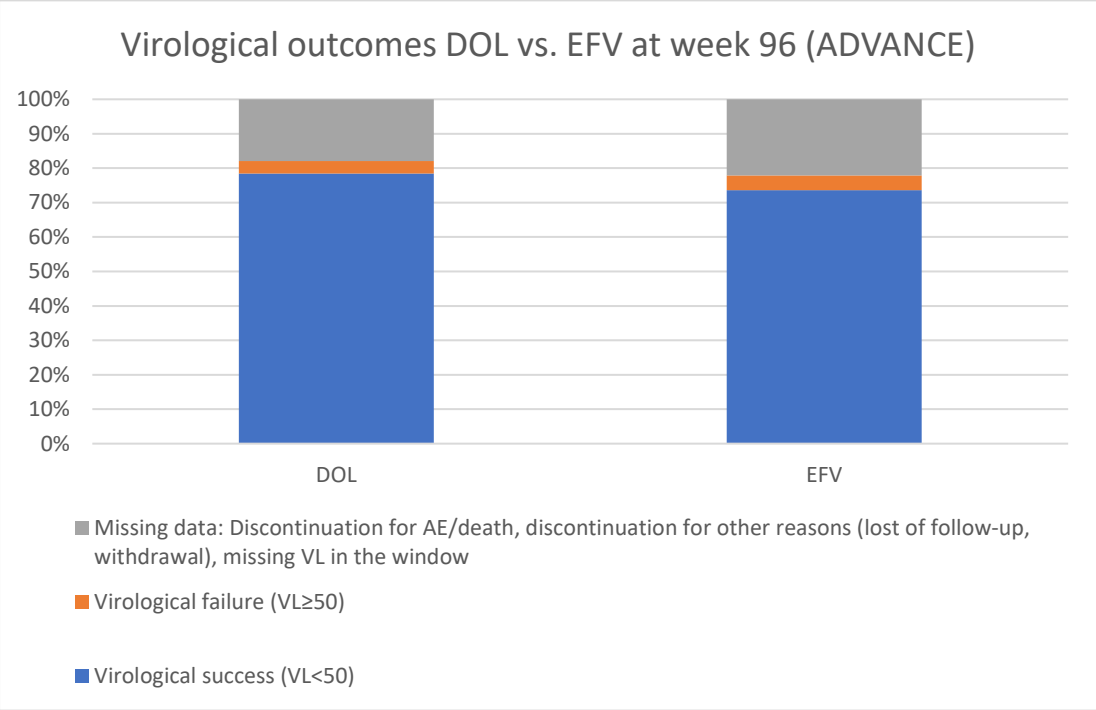
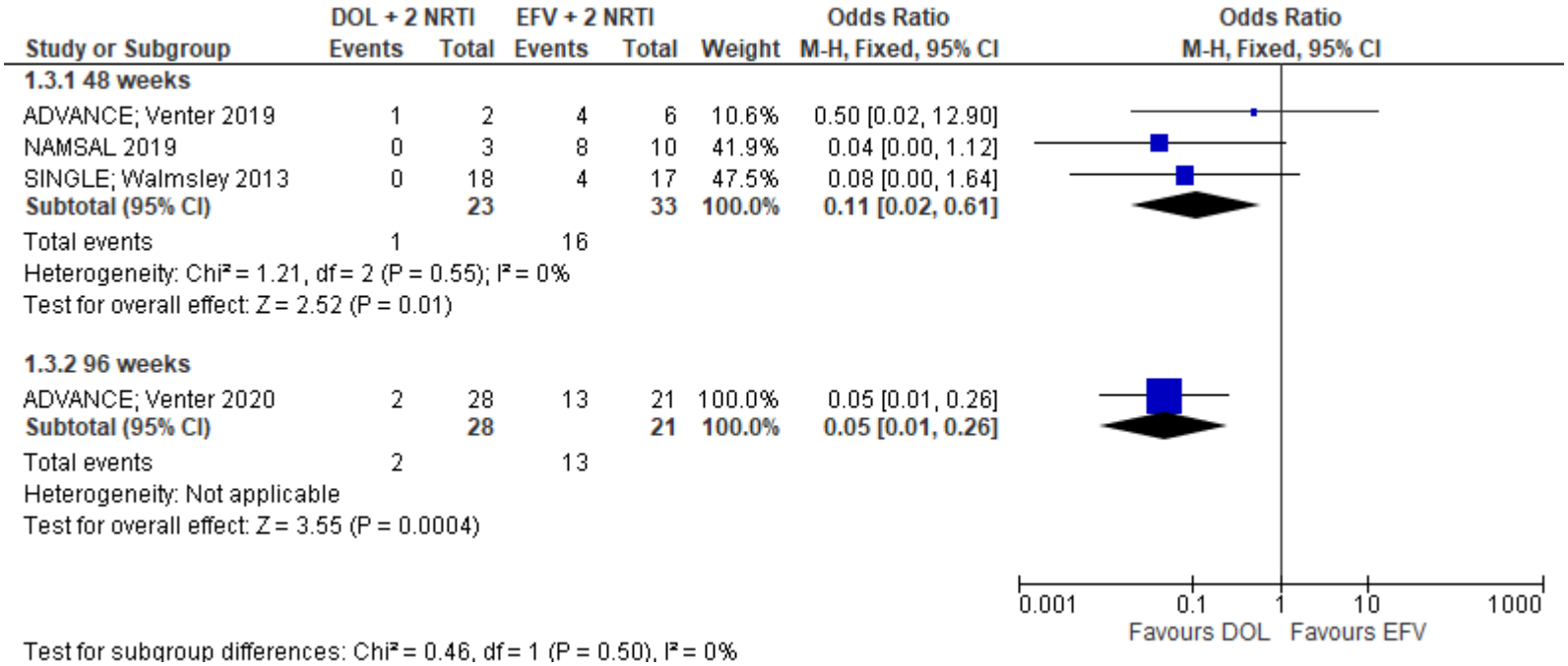


Figure: 2. Success, failure and missing data at 96 weeks



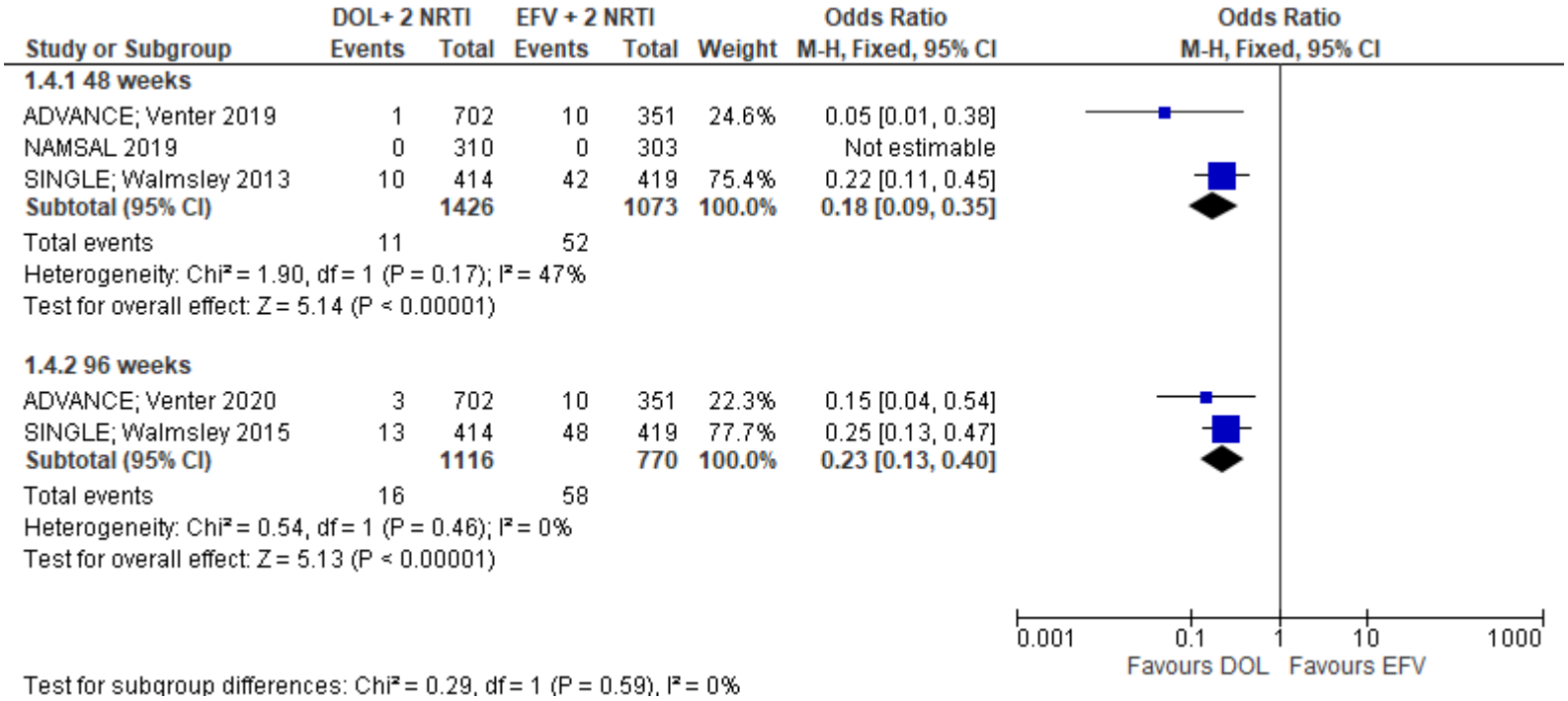
Failing with resistance

Forest plot of comparison: 1 DOL vs EFV + any 2 NRTI, outcome: 1.3 Failure with resistance.



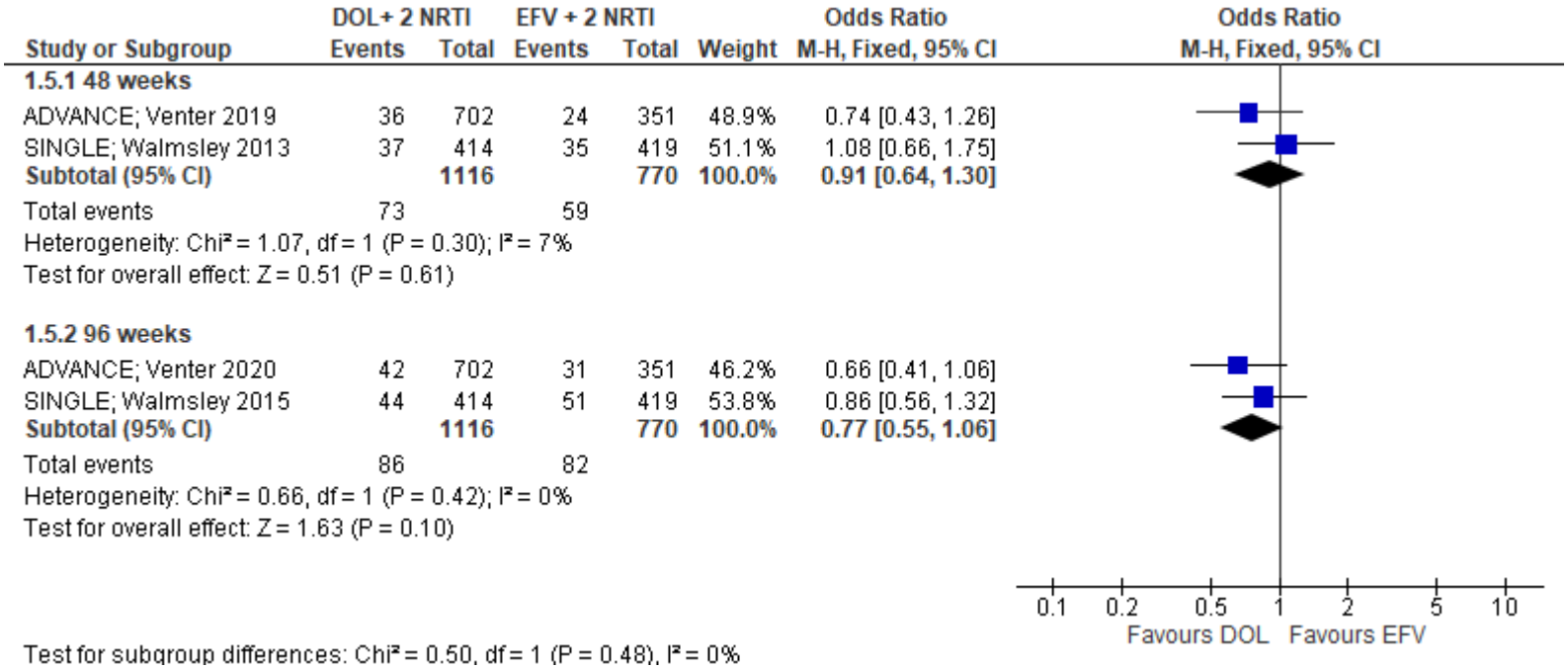
Adverse event (AE)-driven discontinuation

Forest plot of comparison: 1 DOL vs EFV + any 2 NRTI, outcome: 1.4 AE-driven discontinuation.



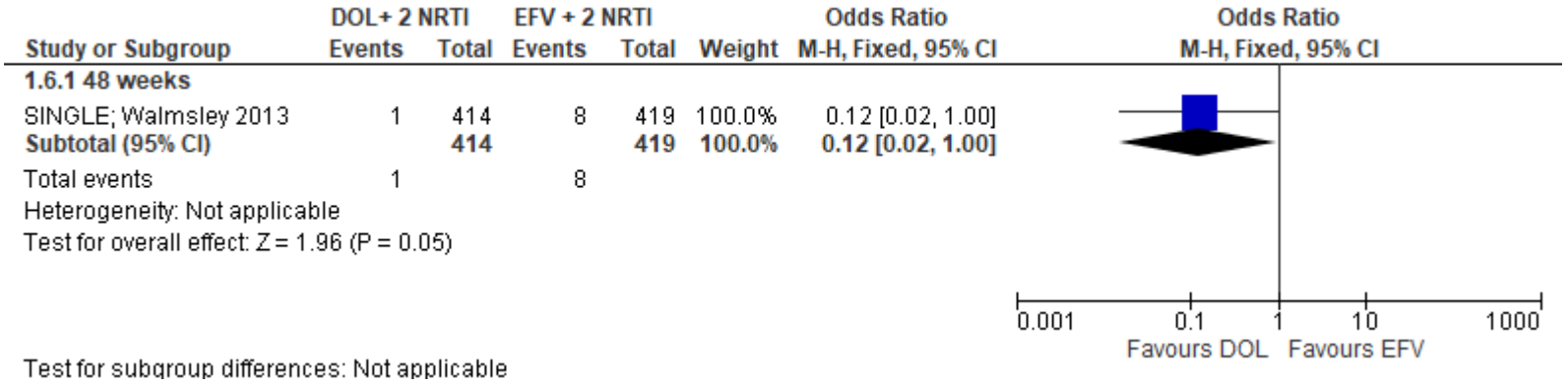
Serious adverse events

Forest plot of comparison: 1 DOL vs EFV + any 2 NRTI, outcome: 1.5 Serious AE.



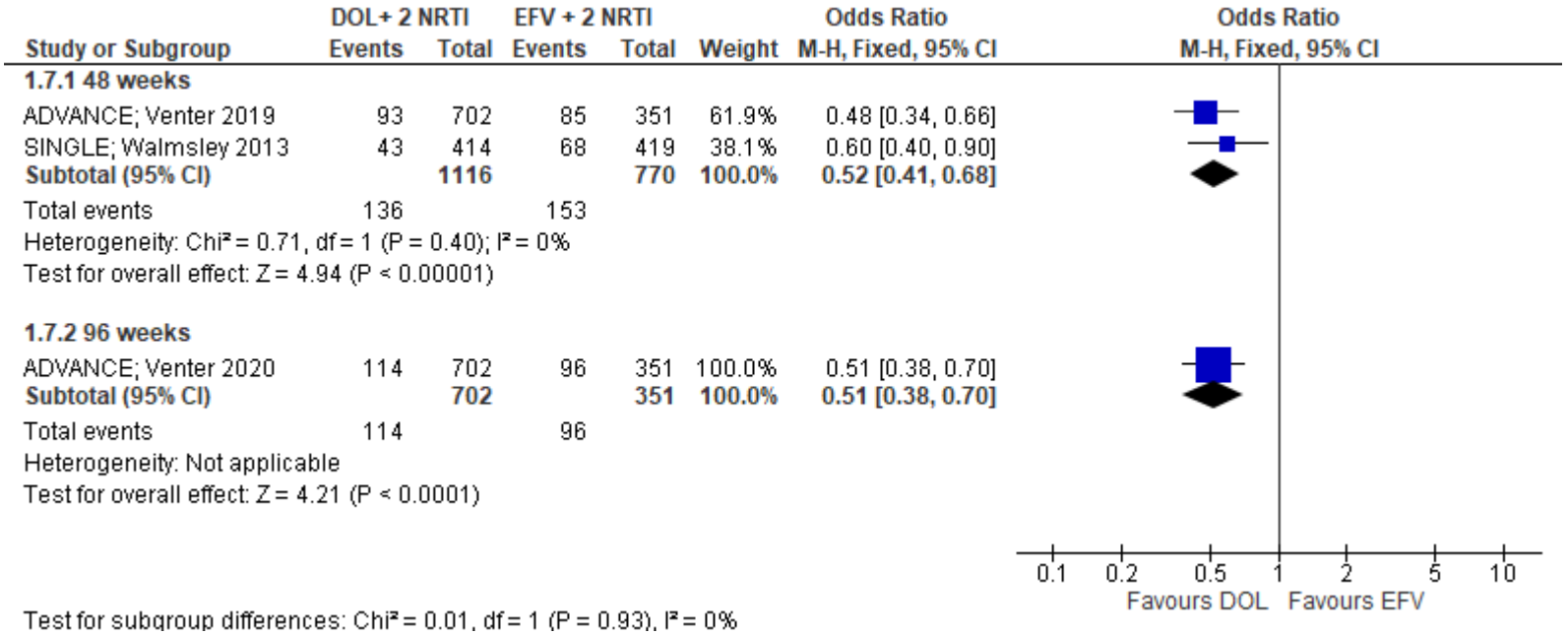
Drug-related SAE

Forest plot of comparison: 1 DOL vs EFV + any 2 NRTI, outcome: 1.6 Drug-related serious AE.



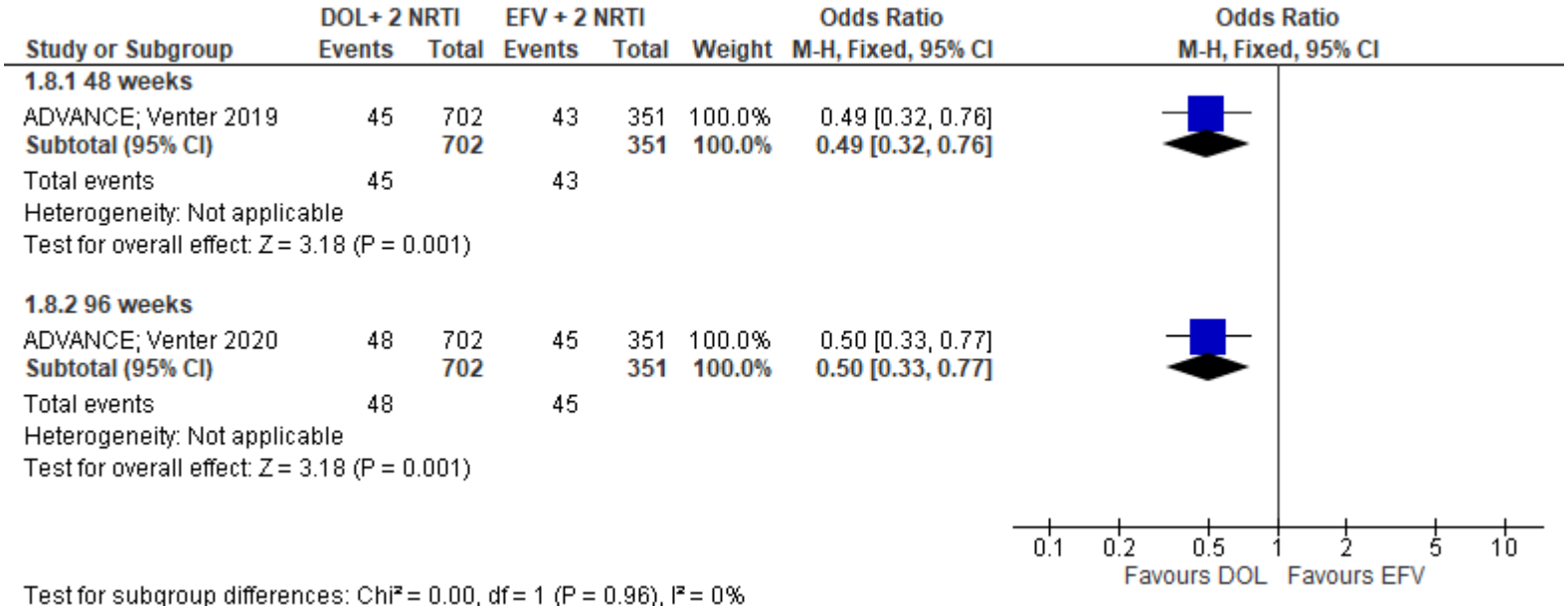
Grade 3/4 AE

Forest plot of comparison: 1 DOL vs EFV + any 2 NRTI, outcome: 1.7 Grade 3/4 AE.



Drug-related Grade 3/4 AE

Forest plot of comparison: 1 DOL vs EFV + any 2 NRTI, outcome: 1.8 Drug-related grade 3/4 AE.



GRADE table for critical outcomes

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with EFV + any 2 NRTI	Risk with DOL				
Virological success - 48 weeks	767 per 1,000	**831 per 1,000** (799 to 857)	**OR 1.49** (1.21 to 1.82)	2499 (3 RCTs)	⨁◯◯◯ Very low[a,b]	
Virological success - 96 weeks	727 per 1,000	**791 per 1,000** (752 to 824)	**OR 1.42** (1.14 to 1.76)	1886 (2 RCTs)	⨁◯◯◯ Very low[a,b]	
Virological failure - 48 weeks	94 per 1,000	**91 per 1,000** (70 to 118)	**OR 0.96** (0.72 to 1.29)	2499 (3 RCTs)	⨁◯◯◯ Very low[b,c,d]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with EFV + any 2 NRTI	Risk with DOL				
Virological failure - 96 weeks	43 per 1,000	**36 per 1,000** (19 to 66)	**OR 0.83** (0.43 to 1.59)	1053 (1 RCT)	⨁⨁◯◯ Low[c,d]	
Failure with resistance - 48 weeks	485 per 1,000	**94 per 1,000** (18 to 365)	**OR 0.11** (0.02 to 0.61)	56 (3 RCTs)	⨁⨁◯◯ Low[b,c]	
Failure with resistance - 96 weeks	619 per 1,000	**75 per 1,000** (16 to 297)	**OR 0.05** (0.01 to 0.26)	49 (1 RCT)	⨁⨁⨁◯ Moderate[c]	
AE-driven discontinuation - 48 weeks	48 per 1,000	**9 per 1,000** (5 to 18)	**OR 0.18** (0.09 to 0.35)	2499 (3 RCTs)	⨁⨁◯◯ Low[b,c]	
AE-driven discontinuation - 96 weeks	75 per 1,000	**18 per 1,000** (10 to 32)	**OR 0.23** (0.13 to 0.40)	1886 (2 RCTs)	⨁⨁◯◯ Low[b,c]	
Serious AE - 48 weeks	77 per 1,000	**70 per 1,000** (50 to 97)	**OR 0.91** (0.64 to 1.30)	1886 (2 RCTs)	⨁◯◯◯ Very low[b,c,d]	
Serious AE - 96 weeks	106 per 1,000	**84 per 1,000** (62 to 112)	**OR 0.77** (0.55 to 1.06)	1886 (2 RCTs)	⨁◯◯◯ Very low[b,c,d]	
Drug-related serious AE - 48 weeks	19 per 1,000	**2 per 1,000** (0 to 19)	**OR 0.12** (0.02 to 1.00)	833 (1 RCT)	⨁⨁◯◯ Low[b,d]	
Grade 3/4 AE - 48 weeks	199 per 1,000	**114 per 1,000** (92 to 144)	**OR 0.52** (0.41 to 0.68)	1886 (2 RCTs)	⨁⨁◯◯ Low[b,c]	
Grade 3/4 AE - 96 weeks	274 per 1,000	**161 per 1,000** (125 to 209)	**OR 0.51** (0.38 to 0.70)	1053 (1 RCT)	⨁⨁⨁◯ Moderate[c]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with EFV + any 2 NRTI	**Risk with DOL**				
Drug-related grade 3/4 AE - 48 weeks	123 per 1,000	**64 per 1,000** (43 to 96)	**OR 0.49** (0.32 to 0.76)	1053 (1 RCT)	⨁⨁⨁◯ Moderate[c]	
Drug-related grade 3/4 AE - 96 weeks	128 per 1,000	**68 per 1,000** (46 to 102)	**OR 0.50** (0.33 to 0.77)	1053 (1 RCT)	⨁⨁⨁◯ Moderate[c]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Difference between groups in numbers with missing data for virological outcomes

b. In SINGLE, only 16% of the participants were women, and the proportion of participants with a CD4+ T-cell count of less than 200 per cubic millimeter was relatively low.

c. Some concerns (open label study)

d. 95% Confidence interval spans 1

2 DOL vs BIC + any 2 NRTI

Two studies were included (NCT02607930; NCT02607956). NCT02607930 data were published for week 48 results (Gallant 2017) and week 96 results (Wohl 2019). Similarly, NCT02607956 data were published for week 48 (Sax 2017) and week 96 results (Stellbrink 2019). This section therefore includes four fully published papers (Gallant 2017, Wohl 2019, Sax 2017 and Stellbrink 2019).
The following Table shows the key features of these studies in terms of their inclusion and exclusion criteria, the characteristics of the population studied, the intervention, comparator and the outcomes reported.

Table 3. Key features of the included studies

Study name/ NCT number	Citation	Inclusion criteria	Exclusions	Population (n; demographics)	Intervention	Comparator	Outcomes
NCT02607930; GS-US-380-1489; 2015-004024-54 (EudraCT Number)	Gallant J, Lazzarin A, Mills A, Orkin C, Podzamczer D, Tebas P, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet (london, england). 2017;390(10107):2063-72.	HIV-1-infected adults (aged ≥18 years) who were previously untreated and had plasma HIV-1 RNA concentrations of 500 copies per mL or more, no hepatitis B virus infection, were HLA-B*5701-negative, had an eGFR of 50 mL/min or more (Cockcroft–Gault	An opportunistic illness indicative of stage 3 HIV diagnosed within the 30 days prior to screening (refer to study protocol) Decompensated cirrhosis (e.g., ascites, encephalopathy, or variceal bleeding) Current alcohol or substance use judged by the Investigator to potentially interfere with	629 participants in 122 outpatient centres in nine countries in Europe, Latin America, and North America. B/F/TAF group (n=314); DTG/ABC/3TC group (n=315) Age (years) 31 (18–71); 32 (18–68) Female 29 (9%); 33 (10%) Male 285 (91%); 282 (90%) Race: White 180 (57%); 179 (57%) Black 114 (36%); 112 (36%) Asian 6 (2%); 10 (3%) American Indian or Alaska Native 2 (1%); 4 (1%) Native Hawaiian or Pacific Islander 1 (<1%); 2 (1%)	Dolutegravir, abacavir and lamivudine	Bictegravir, emtricitabine and tenofovir alafenamide	The primary outcome was the proportion of participants with plasma HIV-1 RNA < 50 copies per mL at week 48, as defined by the US Food and Drug Administration (FDA) snapshot algorithm. Additional prespecified efficacy endpoints included the proportion of

		equation), and had no documented resistance to emtricitabine, tenofovir, abacavir, or lamivudine.	subject study compliance Females who are pregnant (as confirmed by positive serum pregnancy test) Females who are breastfeeding Chronic Hepatitis B Virus (HBV) infection	Other 9 (3%); 8 (3%) Not permitted 2 (1%); 0 Hispanic or Latino 72 (23%); 65 (21%) HIV disease status: Asymptomatic 286 (91%); 286 (91%) Symptomatic 16 (5%); 14 (4%) AIDS 12 (4%); 15 (5%) HIV risk factor: Heterosexual sex 61 (19%); 62 (20%) Homosexual sex 251 (80%); 250 (79%) Intravenous drug use 5 (2%); 4 (1%) HIV-1 RNA (log10 copies per mL) 4·42 (4·03–4·87); 4·51 (4·04–4·87) HIV-1 RNA >100 000 copies per mL 53 (17%); 50 (16%) CD4 count (cells per µL): 443 (299–590); 450 (324–608) <50: 7 (2%); 10 (3%) ≥50 to <200: 29 (9%); 22 (7%) ≥200 to <350: 69 (22%); 58 (18%) ≥350 to <500: 87 (28%); 91 (29%) ≥500: 122 (39%); 134 (43%) Creatinine clearance (mL/min)* 125·9 (107·7–146·3); 123·0 (107·0–144·3) Body-mass index (kg/m²) 25·1 (22·4–			participants with plasma HIV-1 RNA <50 copies per mL at week 48 after imputation of missing-as-failure and missing-as-excluded values.

				28·7); 24·9 (22·5–29·1) Data are median (IQR [range for age]) or n (%). B/F/TAF=bictegravir, emtricitabine, and tenofovir alafenamide. DTG/ABC/3TC=dolutegravir, abacavir, and lamivudine. *Estimated with the Cockcroft–Gault equation.			
	Wohl, DA; Yazdanpanah, Y; Baumgarten, A; Clarke, A; Thompson, MA; Brinson, C; Hagins, D; Ramgopal, MN; Antinori, A; Wei, X; Acosta, R; Collins, SE; Brainard, D; Martin, H. Bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. The lancet. HIV 2019; 6(6): e355-363. DOI: 10.1016/S2352-3018(19)30077-3. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01963192/full	As above	As above	As above	As above	As above	As above
NCT02607956; GS-US-380-1490; 2015-003988-10 (EudraCT Number)	Sax PE, Pozniak A, Montes ML, Koenig E, DeJesus E, Stellbrink HJ, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet (london, england). 2017;390(10107):2073-82.	Adults (aged ≥18 years) with HIV-1 infection who were previously untreated, with plasma HIV-1 RNA levels of at least 500 copies per mL, with estimated glomerular filtration rate (eGFR) of	An opportunistic illness indicative of stage 3 HIV diagnosed within the 30 days prior to screening Decompensated cirrhosis (eg, ascites, encephalopathy, or variceal bleeding) Current alcohol or substance	645 participants at 126 outpatient centres in 10 countries (Australia, Belgium, France, Germany, Italy, Spain, the UK, Dominican Republic, the USA, and Canada). Bictegravir regimen (n=320); Dolutegravir regimen (n=325) Median age, years 33 (27.46); 34 (27.46) Women 40 (13%); 37 (11%) Men 280 (88%); 288 (89%) Race:	Dolutegravir with coformulated emtricitabine and tenofovir alafenamide	Bictegravir, emtricitabine and tenofovir alafenamide	The primary outcome was the proportion of participants who had plasma HIV-1 RNA <50 copies per mL at week 48 as defined by the US FDA snapshot algorithm. Additional prespecified

		at least 30 mL per min (calculated by the Cockcroft-Gault equation), and with virological resistance testing showing sensitivity to emtricitabine and tenofovir	use judged by the Investigator to potentially interfere with subject study compliance Females who are pregnant (as confirmed by positive serum pregnancy test) Females who are breastfeeding	White 183 (57%); 195 (60%) Black 97 (30%); 100 (31%) Asian 7 (2%); 10 (3%) Ethnic origin: Hispanic or Latino 83 (26%); 81 (25%) Region: USA 193 (60%); 193 (59%) Outside the USA 127 (40%); 132 (41%) HIV disease status: Asymptomatic 286 (89%); 288 (89%) Symptomatic 10 (3%); 11 (3%) AIDS 24 (8%); 26 (8%) HIV risk factor:* Heterosexual sex 81 (25%); 77 (24%) Homosexual sex 237 (74%); 250 (77%) Intravenous drug use 3 (1%); 6 (2%) Median HIV-1 RNA log10 copies per mL 4.43 (3.95-4.90); 4.45 (4.03-4.84) HIV-1 RNA concentration: >100 000 to ≤400 000 copies per mL: 54 (17%); 41 (13%) >400 000 copies per mL 12 (4%); 13 (4%) Median CD4 count (cells per µL) 440 (289-591); 441 (297-597) CD4 count (cells per µL):			efficacy endpoints included the proportion of participants with plasma HIV-1 RNA <50 copies per mL at week 48 when imputing missing data as failure (M = F) and missing as excluded (M = E) and changes in log10 HIV-1 RNA and CD4 count from baseline at week 48. Safety outcomes were assessed by changes from baseline in fasting glucose, lipid panels, serum creatinine, and eGFR at week 48.

				<50: 15 (5%); 13 (4%) ≥50 to <200: 29 (9%); 21 (6%) ≥200 to <350: 67 (21%); 77 (24%) ≥350 to <500: 91 (28%); 94 (29%) ≥500: 118 (37%); 120 (37%) Median creatinine clearance (mL/min) 120.4 (100.8-141.8); 120.6 (102.8-145.1) Patients with HIV/HBV co-infection 8 (3%); 6 (2%) Patients with HIV/HCV co-infection 5 (2%); 5 (2%) Median body-mass index (kg/m2) 25.0 (22.2-28.3); 24.6 (22.2-28.0) Data are median (IQR) or n (%), except for age, which is median (range). *A participant may fit more than one HIV risk factor category; therefore, percentages may add to more than 100%. HBV=hepatitis B virus. HCV=hepatitis C virus.			
	Stellbrink, HJ; Arribas, JR; Stephens, JL; Albrecht, H; Sax, PE; Maggiolo, F; Creticos, C; Martorell, CT; Wei, X; Acosta, R; Collins, SE; Brainard, D; Martin, H. Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1	As above	As above	As above	As above	As above	As above

	infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. The lancet. HIV 2019; 6(6): e364-372. DOI: 10.1016/S2352-3018(19)30080-3. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01963191/full						

Table 4. Comparisons included in this section

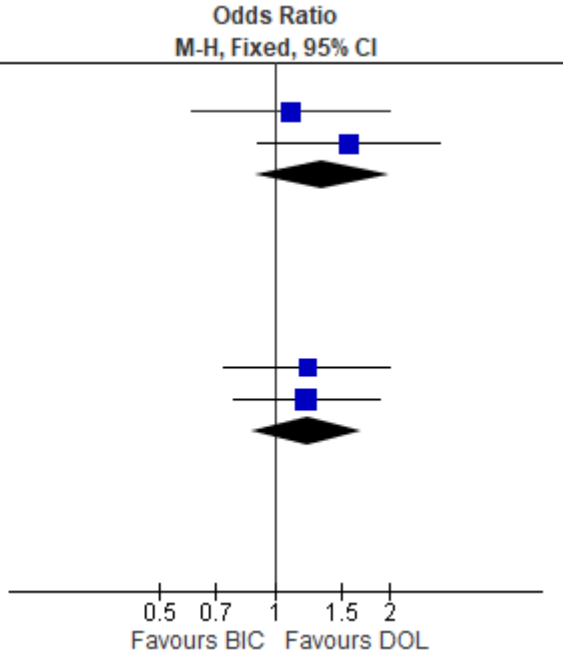
Study name/ NCT number	Intervention (Two NRTI + DOL)	Comparator (2 NRTI + BIC)
NCT02607930; GS-US-380-1489; 2015-004024-54 (EudraCT Number)	Dolutegravir, abacavir and lamivudine	Bictegravir, emtricitabine and tenofovir alafenamide
NCT02607956; GS-US-380-1490; 2015-003988-10 (EudraCT Number)	Dolutegravir, emtricitabine and tenofovir alafenamide	Bictegravir, emtricitabine and tenofovir alafenamide

Virological success, failure and missing data

Forest plot of comparison: 2 DOL vs BIC + any 2 NRTI, outcome: 2.1 Virological success.

Study or Subgroup	DOL + 2 NRTI Events	Total	BIC + 2 NRTI Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 48 weeks						
NCT02607930; Gallant 2017	293	315	290	314	49.9%	1.10 [0.60, 2.01]
NCT02607956; Sax 2017	302	325	286	320	50.1%	1.56 [0.90, 2.71]
Subtotal (95% CI)		**640**		**634**	**100.0%**	**1.33 [0.89, 2.00]**
Total events	595		576			
Heterogeneity: Chi² = 0.70, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 1.39 (P = 0.17)						
2.1.2 96 weeks						
NCT02607930; Wohl 2019	283	315	276	314	43.3%	1.22 [0.74, 2.00]
NCT02607956; Stellbrink 2019	281	325	269	320	56.7%	1.21 [0.78, 1.87]
Subtotal (95% CI)		**640**		**634**	**100.0%**	**1.21 [0.87, 1.69]**
Total events	564		545			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.16 (P = 0.25)						

Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.73), I² = 0%



Forest plot of comparison: 2 DOL vs BIC + any 2 NRTI, outcome: 2.2 Virological failure.

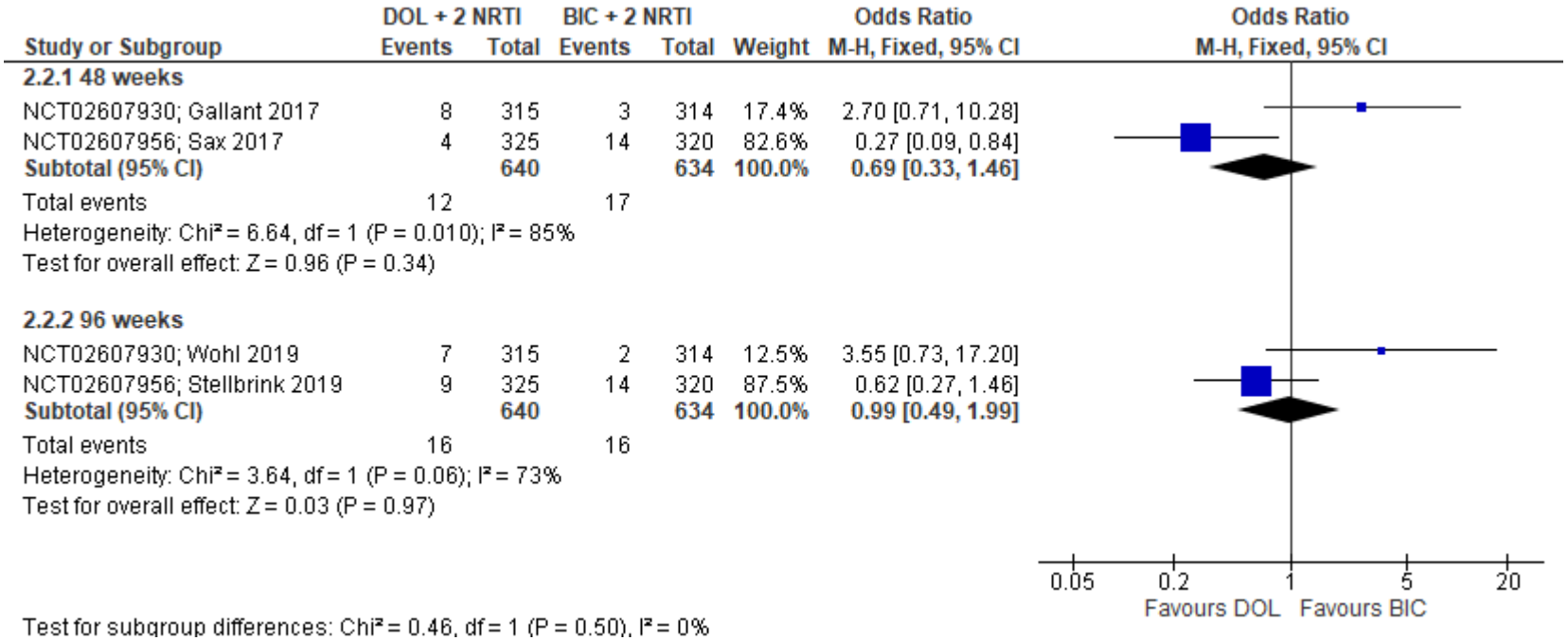


Figure: 3. Success, failure and missing data at 48 weeks

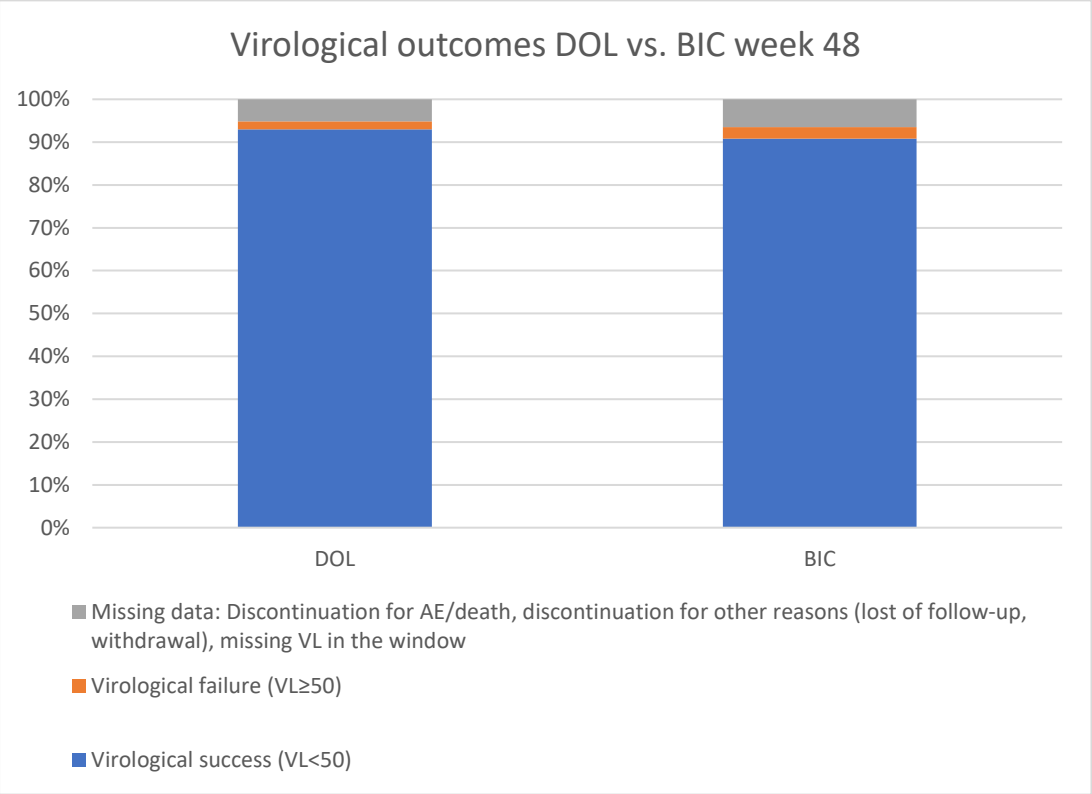
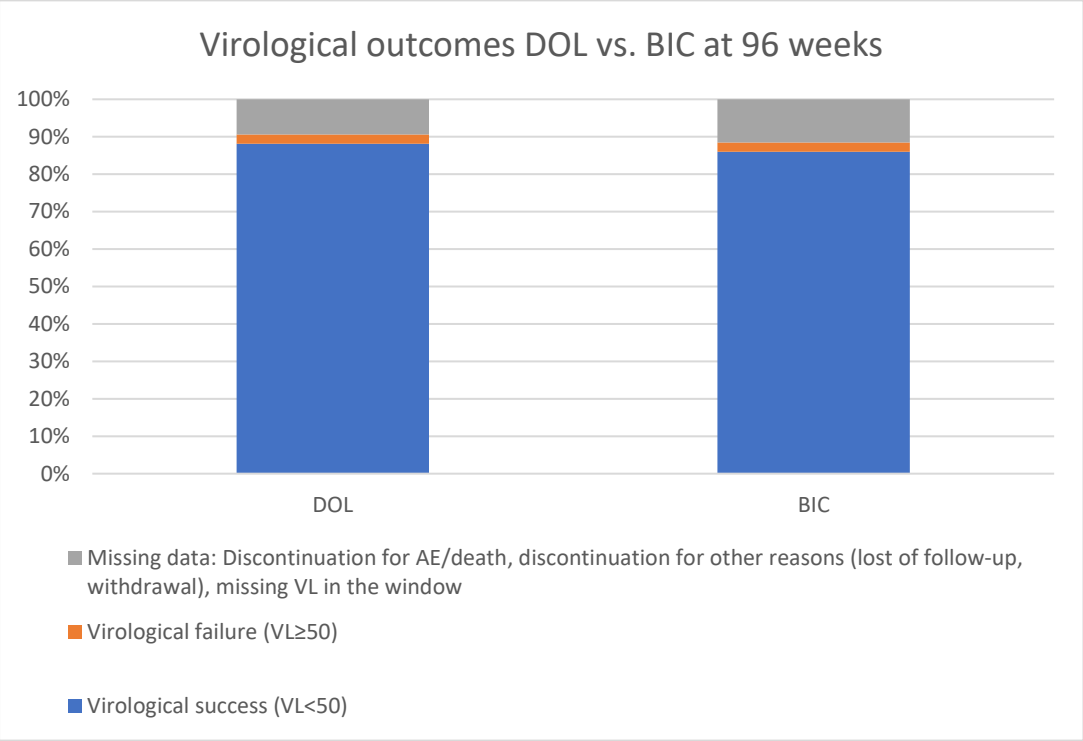


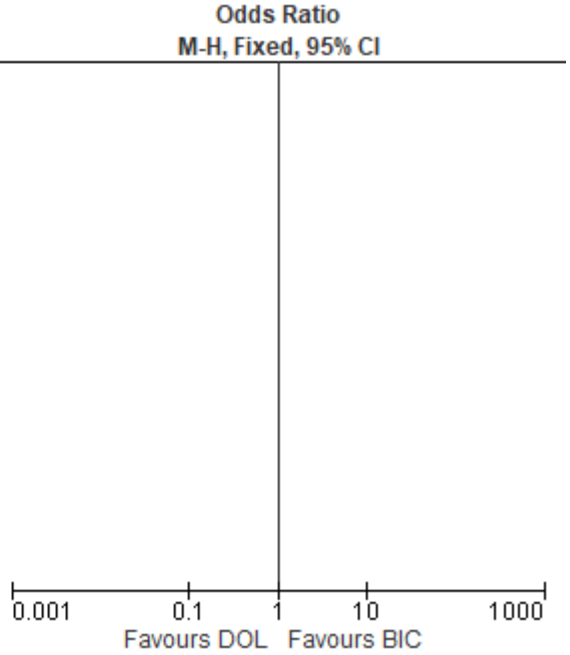
Figure: 4. Success, failure and missing data at 96 weeks



Failing with resistance

Forest plot of comparison: 2 DOL vs BIC + any 2 NRTI, outcome: 2.3 Failure with resistance.

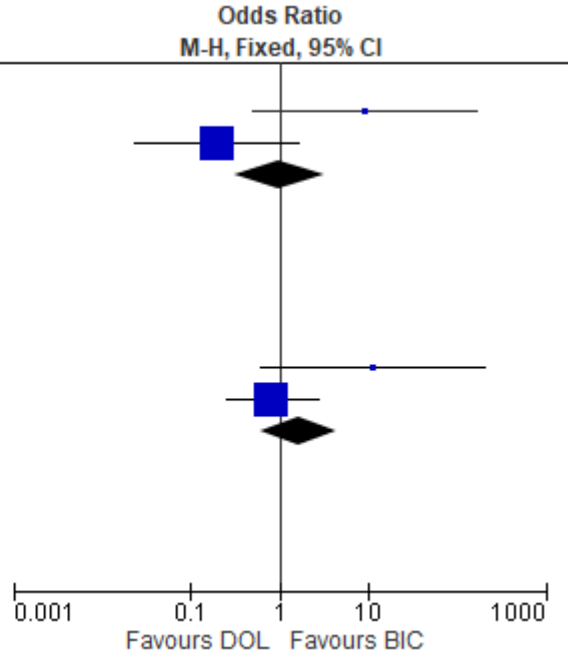
Study or Subgroup	DOL + 2 NRTI Events	Total	BIC + 2 NRTI Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.3.1 48 weeks						
NCT02607930; Gallant 2017	0	4	0	1		Not estimable
NCT02607956; Sax 2017	0	5	0	7		Not estimable
Subtotal (95% CI)		**9**		**8**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.3.2 96 weeks						
NCT02607930; Wohl 2019	0	5	0	0		Not estimable
NCT02607956; Stellbrink 2019	0	5	0	7		Not estimable
Subtotal (95% CI)		**10**		**7**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Adverse event (AE)-driven discontinuation

Forest plot of comparison: 2 DOL vs BIC + any 2 NRTI, outcome: 2.4 AE-driven discontinuation.

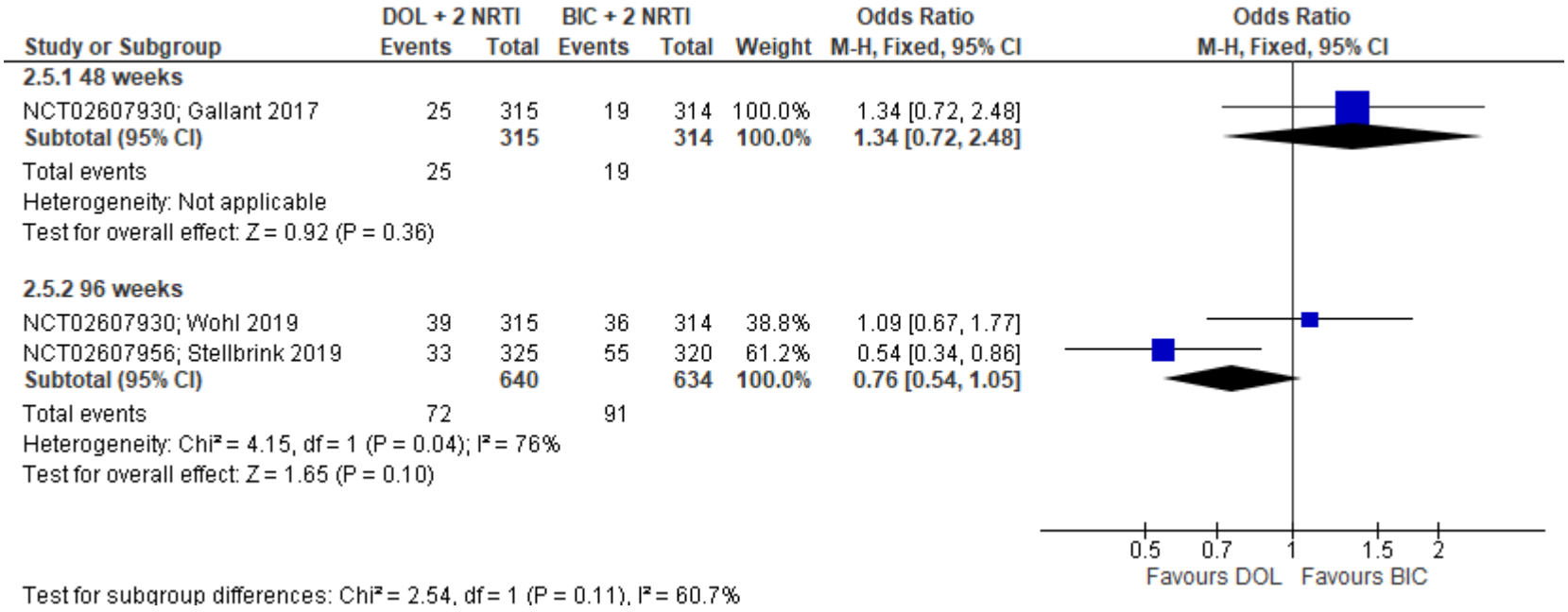
Study or Subgroup	DOL + 2 NRTI Events	Total	BIC + 2 NRTI Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.4.1 48 weeks						
NCT02607930; Gallant 2017	4	315	0	314	8.9%	9.09 [0.49, 169.48]
NCT02607956; Sax 2017	1	325	5	320	91.1%	0.19 [0.02, 1.67]
Subtotal (95% CI)		**640**		**634**	**100.0%**	**0.99 [0.30, 3.23]**
Total events	5		5			
Heterogeneity: Chi² = 4.40, df = 1 (P = 0.04); I² = 77%						
Test for overall effect: Z = 0.02 (P = 0.99)						
2.4.2 96 weeks						
NCT02607930; Wohl 2019	5	315	0	314	7.6%	11.14 [0.61, 202.35]
NCT02607956; Stellbrink 2019	5	325	6	320	92.4%	0.82 [0.25, 2.71]
Subtotal (95% CI)		**640**		**634**	**100.0%**	**1.61 [0.60, 4.30]**
Total events	10		6			
Heterogeneity: Chi² = 2.94, df = 1 (P = 0.09); I² = 66%						
Test for overall effect: Z = 0.94 (P = 0.35)						



Test for subgroup differences: Chi² = 0.38, df = 1 (P = 0.54), I² = 0%

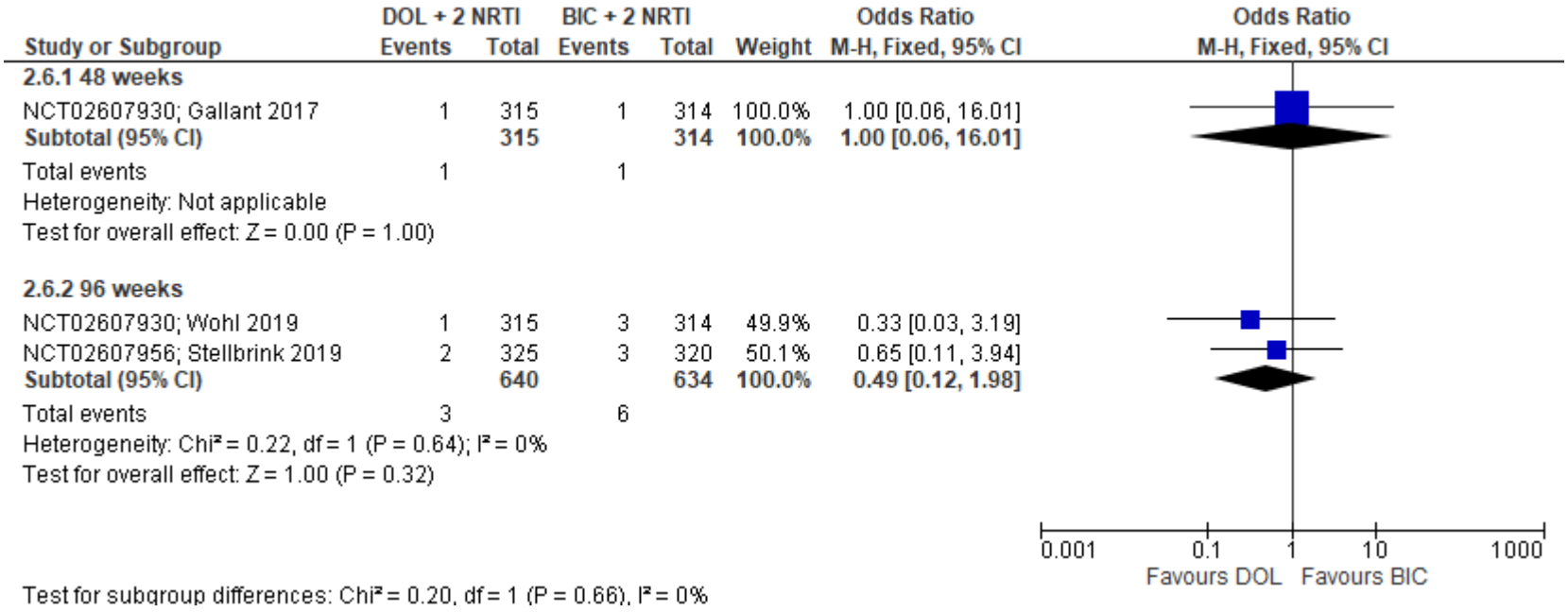
Serious adverse events

Forest plot of comparison: 2 DOL vs BIC + any 2 NRTI, outcome: 2.5 Serious AE.



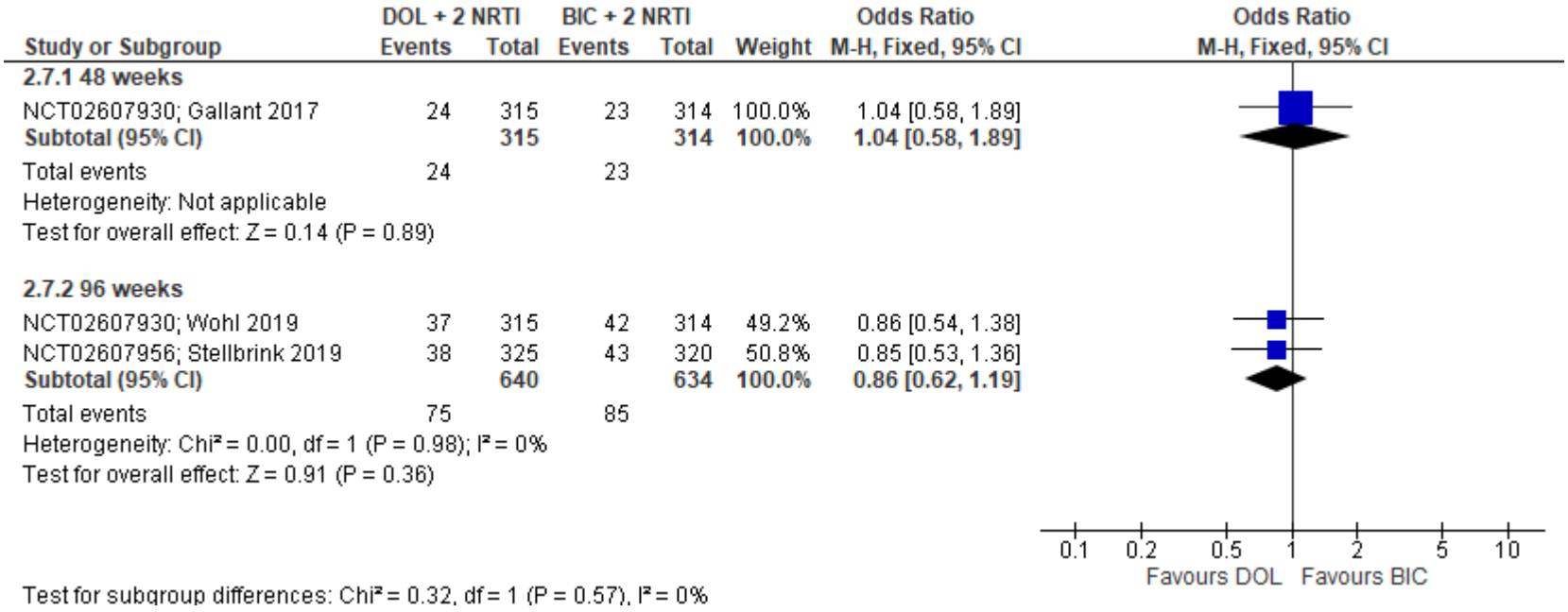
Drug-related SAE

Forest plot of comparison: 2 DOL vs BIC + any 2 NRTI, outcome: 2.6 Drug-related serious AE.



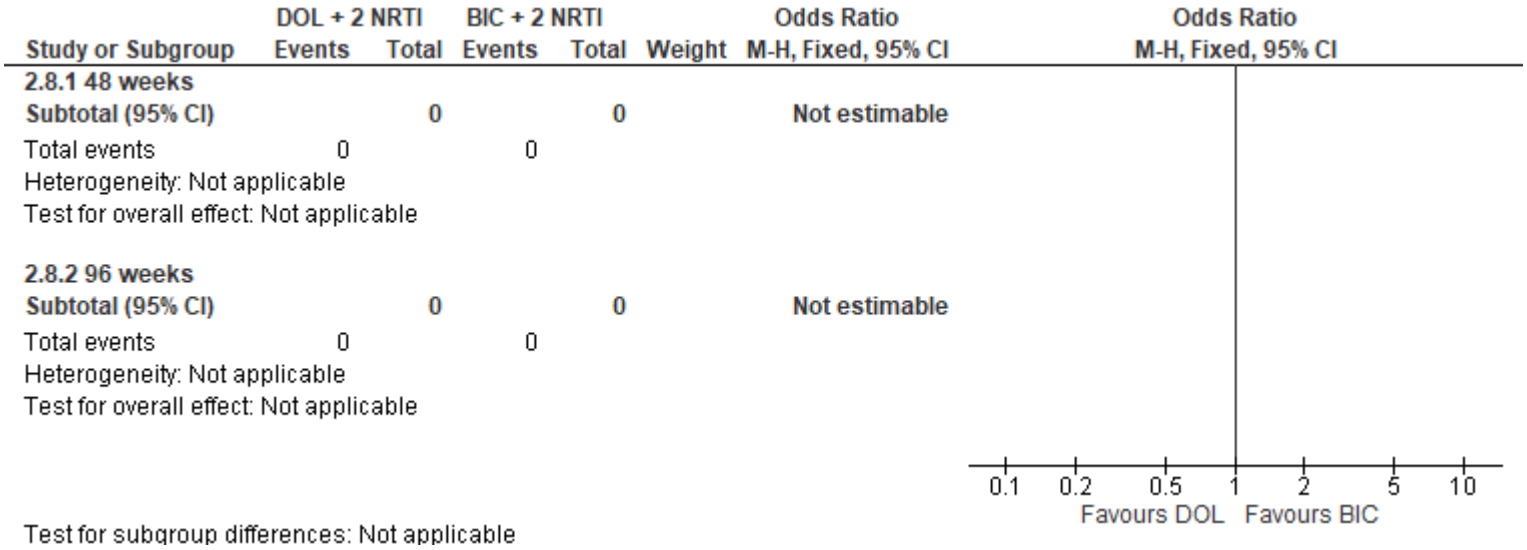
Grade 3/4 AE

Forest plot of comparison: 2 DOL vs BIC + any 2 NRTI, outcome: 2.7 Grade 3/4 AE.



Drug-related Grade 3/4 AE

Forest plot of comparison: 2 DOL vs BIC + any 2 NRTI, outcome: 2.8 Drug-related grade 3/4 AE.



GRADE table for critical outcomes

Outcomes	Anticipated absolute effects* (95% CI) Risk with BIC + any 2 NRTI	Anticipated absolute effects* (95% CI) Risk with DOL	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Virological success - 48 weeks	909 per 1,000	**930 per 1,000** (898 to 952)	**OR 1.33** (0.89 to 2.00)	1274 (2 RCTs)	⨁⨁◯◯ Low[a,b]	
Virological success - 96 weeks	860 per 1,000	**881 per 1,000** (842 to 912)	**OR 1.21** (0.87 to 1.69)	1274 (2 RCTs)	⨁◯◯◯ Very low[a,b,c]	
Virological failure - 48 weeks	27 per 1,000	**19 per 1,000** (9 to 39)	**OR 0.69** (0.33 to 1.46)	1274 (2 RCTs)	⨁◯◯◯ Very low[a,b,d]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with BIC + any 2 NRTI	Risk with DOL				
Virological failure - 96 weeks	25 per 1,000	**25 per 1,000** (13 to 49)	**OR 0.99** (0.49 to 1.99)	1274 (2 RCTs)	⨁◯◯◯ Very low[a,b,d]	
Failure with resistance - 48 weeks	not pooled	not pooled	not pooled	17 (2 RCTs)	-	No events in either group
Failure with resistance - 96 weeks	not pooled	not pooled	not pooled	17 (2 RCTs)	-	No events in either group
AE-driven discontinuation - 48 weeks	8 per 1,000	**8 per 1,000** (2 to 25)	**OR 0.99** (0.30 to 3.23)	1274 (2 RCTs)	⨁◯◯◯ Very low[a,b,d]	
AE-driven discontinuation - 96 weeks	9 per 1,000	**15 per 1,000** (6 to 39)	**OR 1.61** (0.60 to 4.30)	1274 (2 RCTs)	⨁◯◯◯ Very low[a,b,d]	
Serious AE - 48 weeks	61 per 1,000	**79 per 1,000** (44 to 138)	**OR 1.34** (0.72 to 2.48)	629 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Serious AE - 96 weeks	144 per 1,000	**113 per 1,000** (83 to 150)	**OR 0.76** (0.54 to 1.05)	1274 (2 RCTs)	⨁◯◯◯ Very low[a,b,d]	
Drug-related serious AE - 48 weeks	3 per 1,000	**3 per 1,000** (0 to 49)	**OR 1.00** (0.06 to 16.01)	629 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Drug-related serious AE - 96 weeks	9 per 1,000	**5 per 1,000** (1 to 19)	**OR 0.49** (0.12 to 1.98)	1274 (2 RCTs)	⨁⨁◯◯ Low[a,b]	
Grade 3/4 AE - 48 weeks	73 per 1,000	**76 per 1,000** (44 to 130)	**OR 1.04** (0.58 to 1.89)	629 (1 RCT)	⨁⨁◯◯ Low[a,b]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with BIC + any 2 NRTI	**Risk with DOL**				
Grade 3/4 AE - 96 weeks	134 per 1,000	**118 per 1,000** (88 to 156)	**OR 0.86** (0.62 to 1.19)	1274 (2 RCTs)	⨁⨁◯◯ Low[a,b]	
Drug-related grade 3/4 AE - 48 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome
Drug-related grade 3/4 AE - 96 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Small proportion of study participants were women or had advanced HIV disease

b. 95% Confidence interval includes 1

c. >10% missing data

d. I^2 >60%

3 DOL vs b/PI + any 2 NRTI

Two studies were included. The results of the ARIA study were reported at 48 weeks (Orrell 2017). The results of the FLAMNIGO study were reported at 48 weeks (Clotet 2014) and at 96 weeks (Molina 2015).

Table 5. Key features of the included studies

Study name/ NCT number	Citation	Inclusion criteria	Exclusions	Population (n; demographics)	Intervention	Comparator	Outcomes
NCT01910402; ARIA	Orrell C, Hagins DP, Belonosova E, Porteiro N, Walmsley S, Falcó V, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. The lancet HIV. 2017;4(12):e536-e46.	Women aged ≥18 years who had HIV-1 RNA viral loads of ≥500 copies per mL, received ≤10 days of previous ART, tested negative for the HLA-B*5701 allele; had to test negative for pregnancy and agree to protocol-defined approved contraception method.	Participants were excluded if they had any evidence of active US Centers for Disease Control and Prevention (CDC) Category C HIV disease, hepatic impairment, creatinine clearance of less than 50 mL/min, or primary viral resistance based on the presence of any major resistance-associated mutation according to the 2013 International AIDS Society guidelines. Participants who became pregnant during the study were required to withdraw.	499 participants in 86 hospital and university infectious disease clinics, local health clinics, and private infectious disease clinics in 12 countries and one US territory, in North America, South America, Europe, Africa, and Asia. Dolutegravir group (n=248); Atazanavir group (n=247) Mean age, years (SD) 38·1 (11.15); 37·8 (10.14) Ethnic origin: Black 102 (41%); 108 (44%) White 115 (46%); 107 (43%) Asian 22 (9%); 23 (9%) Other 9 (4%); 9 (4%) Country or territory of origin: USA* 62 (25%); 69 (28%) Puerto Rico 0; 2 (<1%)	Dolutegravir plus abacavir and lamivudine	Ritonavir-boosted atazanavir plus coformulated tenofovir disoproxil fumarate and emtricitabine	The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies per mL at week 48 assessed with the US FDA snapshot algorithm for the intention-to-treat exposed (ITT-E) population, defined as all participants who received at least one dose of study medication. Secondary efficacy endpoints included the proportion of participants with plasma HIV-1 RNA <50 copies per mL and <400 copies per mL over time, absolute values and change from baseline in plasma HIV-1 RNA over time, CD4 lymphocyte cell counts and changes

				South Africa 33 (13%); 33 (13%) Spain 23 (9%); 31 (13%) Russia 28 (11%); 22 (9%) Argentina 24 (10%); 20 (8%) Thailand 19 (8%); 21 (9%) Italy 17 (7%); 11 (4%) UK 14 (6%); 11 (4%) Canada 11 (4%); 9 (4%) France* 7 (3%); 8 (3%) Mexico 6 (2%); 5 (2%) Portugal 4 (2%); 5 (2%) Hepatitis C infection 16 (6%); 21 (9%) CDC category of HIV-1 infection: Asymptomatic 210 (85%); 208 (84%) Symptomatic, not AIDS 27 (11%); 30 (12%) AIDS 11 (4%); 9 (4%) HIV-1 RNA concentration: ≤100 000 copies per mL 179 (72%); 181 (73%) >100 000 copies per mL 69 (28%); 66 (27%) Median, log copies per mL 4·410 (3·91–			from baseline, and incidence of disease progression (HIV-associated conditions, AIDS, and death). Safety endpoints were identified by the following: serious adverse events; haematology, blood chemistry, and fasting lipid assessments; physical assessments; urinalysis results; assessment and documentation of all concomitant medications and blood products received; and monitoring of suicidal intent with the Columbia Suicide-Severity Rating Scale. Other endpoints included the incidence of treatment-emergent genotypic and phenotypic resistance in patients who met confirmed virological withdrawal criteria, and health outcome measures of quality of life and treatment satisfaction.

				5·09); 4·430 (3·92–5·05) CD4 count: <50 cells per µL 9 (4%); 15 (6%) 50 to <200 cells per µL 55 (22%); 34 (14%) 200 to <350 cells per µL 66 (27%); 74 (30%) 350 to <500 cells per µL 56 (23%); 65 (26%) ≥500 cells per µL 62 (25%); 59 (24%) Median cells per µL 340·0 (197·0–497·5); 350·0 (241·0–487·0) Known HIV risk factors†: Heterosexual contact 233 (94%); 233 (94%) Homosexual contact 1 (<1%); 2 (1%) Injectable drug use 12 (5%); 8 (3%) Transfusion 5 (2%); 2 (1%) Other 5 (2%); 5 (2%) Data are n (%) unless otherwise indicated. CDC=US Centers for Disease Control and Prevention. *Four participants did not receive treatment: USA n=3, France n=1. †Some patients			

				had more than one risk factor.			
NCT01449929; FLAMINGO	Clotet B, Feinberg J, van Lunzen J, Khuong-Josses MA, Antinori A, Dumitru I, Pokrovskiy V, Fehr J, Ortiz R, Saag M, Harris J, Brennan C, Fujiwara T, Min S; ING114915 Study Team. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet. 2014 Jun 28;383(9936):2222-31. doi: 10.1016/S0140-6736(14)60084-2. Epub 2014 Apr 1. Erratum in: Lancet. 2015 Jun 27;385(9987):2576. PMID: 24698485.	≥18 years; had a concentration of plasma HIV-1 RNA ≥1000 copies/mL, no previous treatment with antiretroviral therapy, and no primary resistance to NRTIs or protease inhibitors	Patients with active disease of category C from the Centers for Disease Control and Prevention, and defi ned laboratory values or medical characteristics such as pregnancy, moderate or severe hepatic impairment, an anticipated need for hepatitis C treatment during the study, estimated creatinine clearance of <50 mL/min (due to use of fixed-dose NRTI combinations), recent (within the past 5 years) or ongoing malignancy, or treatment with an HIV-1 vaccine within 90 days of screening or with any immunomodulator within 28 days. Patients could receive abacavir–lamivudine only after screening negative for the HLA-B57*01 allele.	488 participants. Dolutegravir (n=242); Darunavir/ritonavir (n=242) Median age (range), years: 34 (18–67); 34 (19–67) Male sex 211 (87%); 201 (83%) Race: White 173 (71%); 176 (73%) African American or African heritage 60 (25%); 53 (22%) Other 8 (3%); 13 (5%) Baseline HIV-1 RNA Median (IQR), log10 copies per mL: 4.49 (4.02–5.02); 4.48 (4.01–5.01) >100 000 copies per mL: 61 (25%); 61 (25%) Baseline CD4 cell count Median (IQR), cells per µL: 390 (290–500); 400 (300–530)	Dolutegravir with investigator-selected combination tenofovir and emtricitabine or combination abacavir and lamivudine	Darunavir plus ritonavir with investigator-selected combination tenofovir and emtricitabine or combination abacavir and lamivudine	Primary endpoint: the proportion of patients with a concentration of HIV-1 RNA lower than 50 copies per mL at week 48, using the US Food and Drug Administration (FDA) snapshot (missing, switch, or discontinuation equals failure; MSDF) algorithm. Secondary: changes from baseline in CD4 cell counts, incidence and severity of adverse events, changes in laboratory variables (such as fasting low-density lipoprotein [LDL] cholesterol), time to virological suppression, and treatment-emergent genotypic or phenotypic evidence of resistance; disease progression, proportion of patients who discontinued treatment because of adverse events, and health outcomes

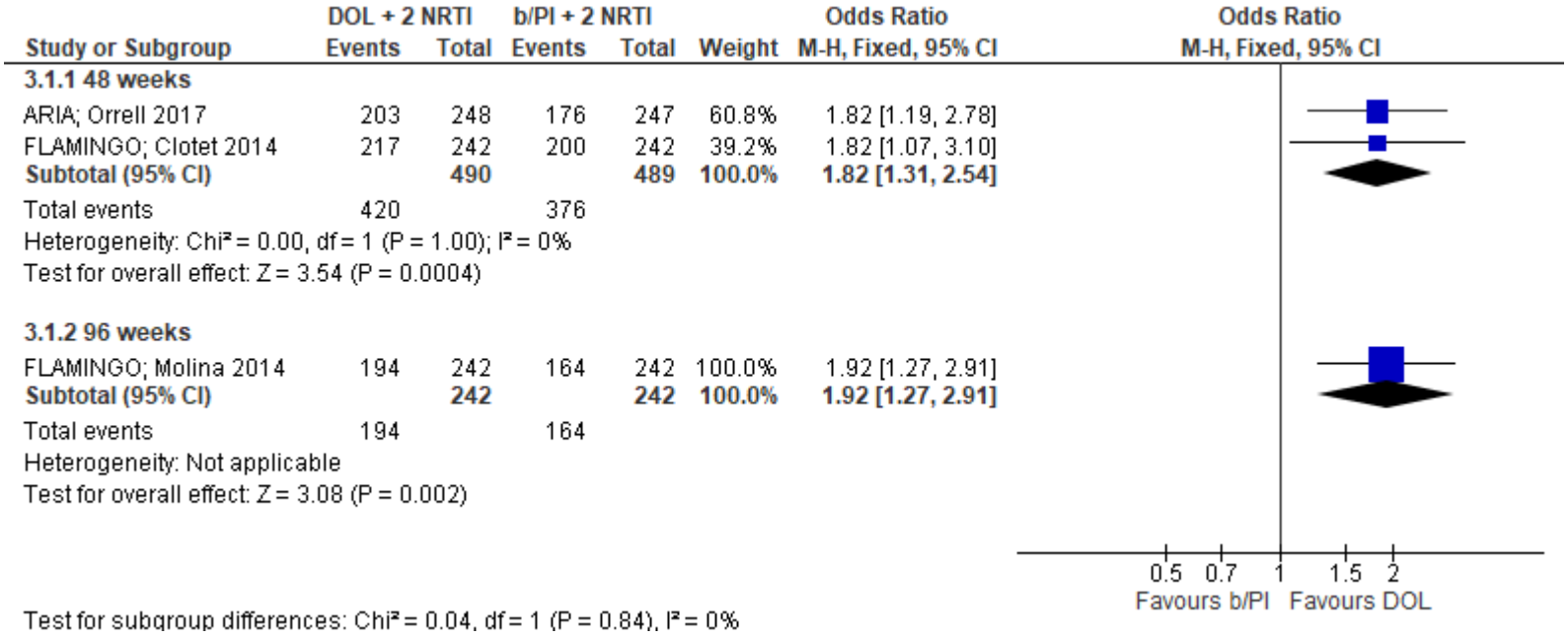
							measures, including the EuroQol five dimension (EQ-5D), HIV Treatment Satisfaction Questionnaire, and Symptom Distress Module.
	Molina JM, Clotet B, van Lunzen J, Lazzarin A, Cavassini M, Henry K, Kulagin V, Givens N, de Oliveira CF, Brennan C; FLAMINGO study team. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study. Lancet HIV. 2015 Apr;2(4):e127-36. doi: 10.1016/S2352-3018(15)00027-2. Epub 2015 Mar 10. Erratum in: Lancet HIV. 2015 Apr;2(4):e126. PMID: 26424673.	As above	As above	As above	As above	As above	As above

Table 6. Comparisons included in this section

Study name/ NCT number	Intervention (Two NRTI + DOL)	Comparator (2 NRTI + b/PI)
NCT01910402; ARIA	Dolutegravir, abacavir and lamivudine	Ritonavir-boosted atazanavir, tenofovir disoproxil fumarate and emtricitabine
NCT01449929; FLAMINGO	Dolutegravir with investigator-selected combination tenofovir (DF) and emtricitabine or combination abacavir and lamivudine	Darunavir plus ritonavir with investigator-selected combination tenofovir (DF) and emtricitabine or combination abacavir and lamivudine

Virological success, failure and missing data

Forest plot of comparison: 3 DOL vs b/PI + any 2 NRTI, outcome: 3.1 Virological success.



Of note, the ARIA study reported superiority primarily driven by the lower rates of adverse-event-related discontinuations and virological non-response in the dolutegravir group.

Similarly, the FLAMINGO study reported that discontinuation due to adverse events or stopping criteria at 48 weeks was less frequent for dolutegravir (four [2%] patients) than for darunavir plus ritonavir (ten [4%] patients) and contributed to the difference in response rates. This study also reported that part of

the difference in the virological response rates at 96 weeks was driven by a higher percentage of discontinuations for other reasons (e.g., lost to follow-up) in the darunavir plus ritonavir group than in the dolutegravir group.

Forest plot of comparison: 3 DOL vs b/PI + any 2 NRTI, outcome: 3.2 Virological failure.

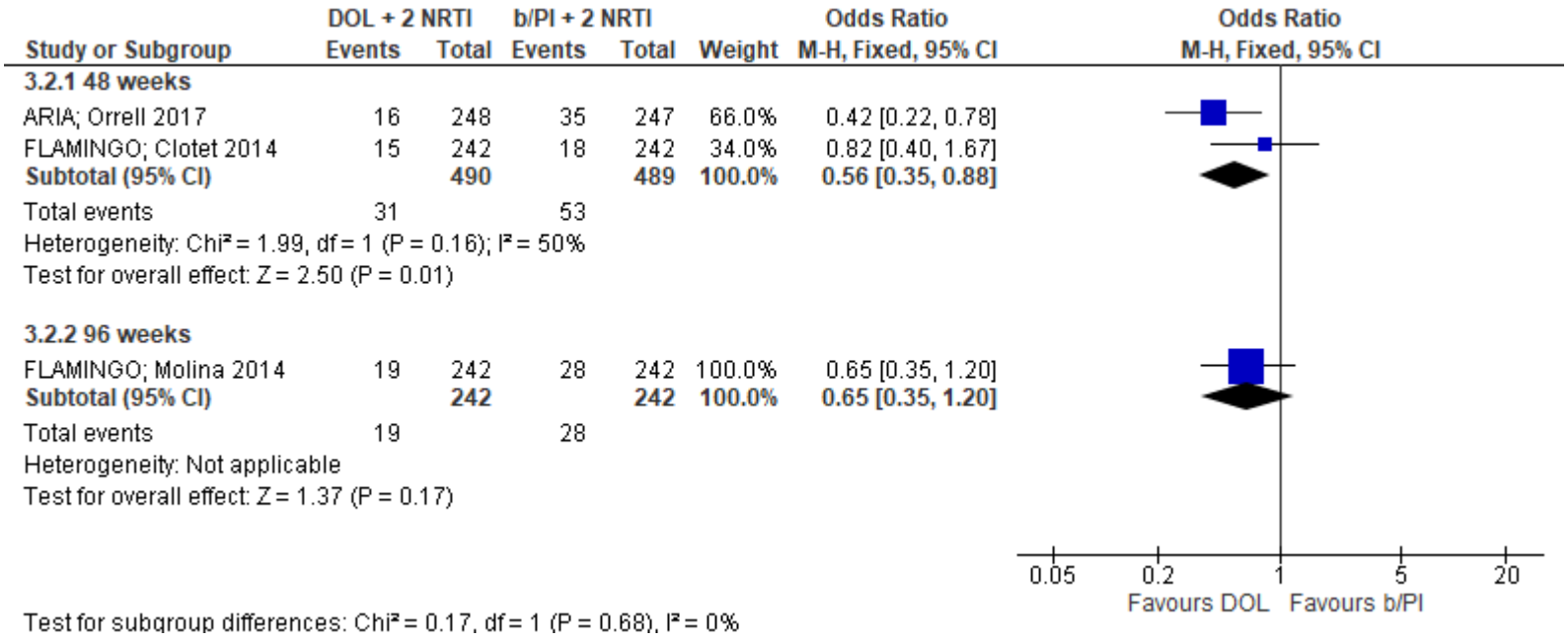


Figure 5. Success, failure and missing data at 48 weeks

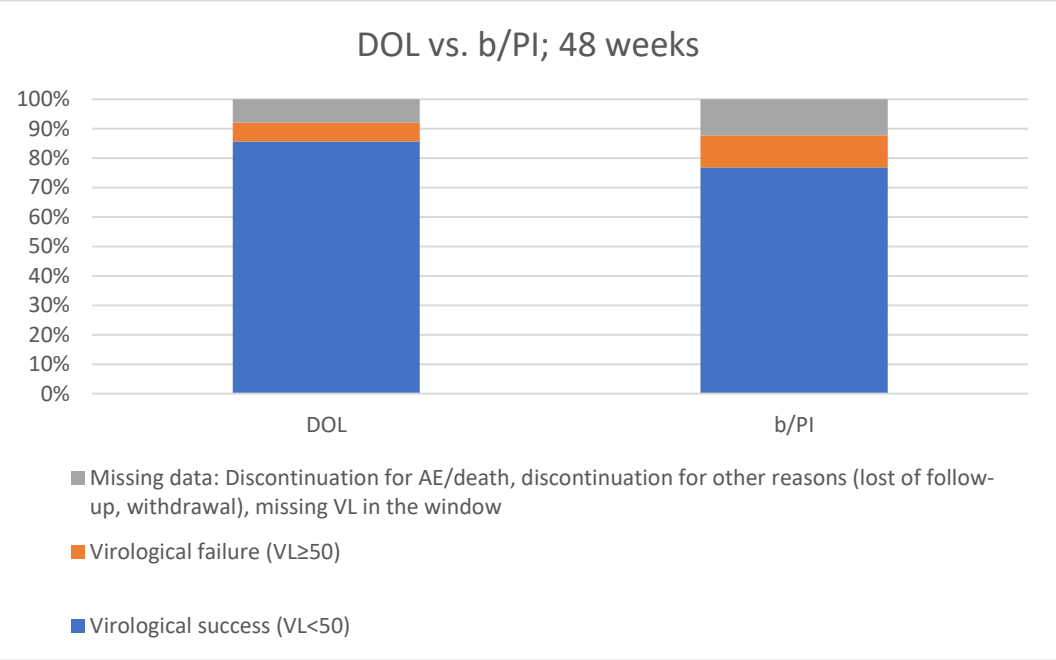
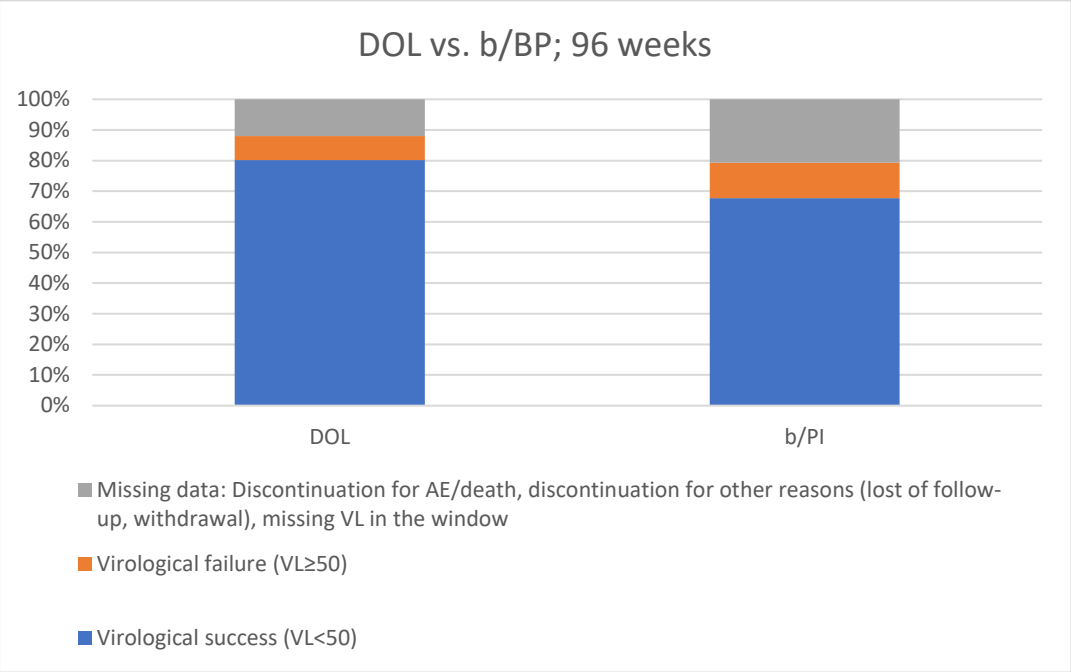
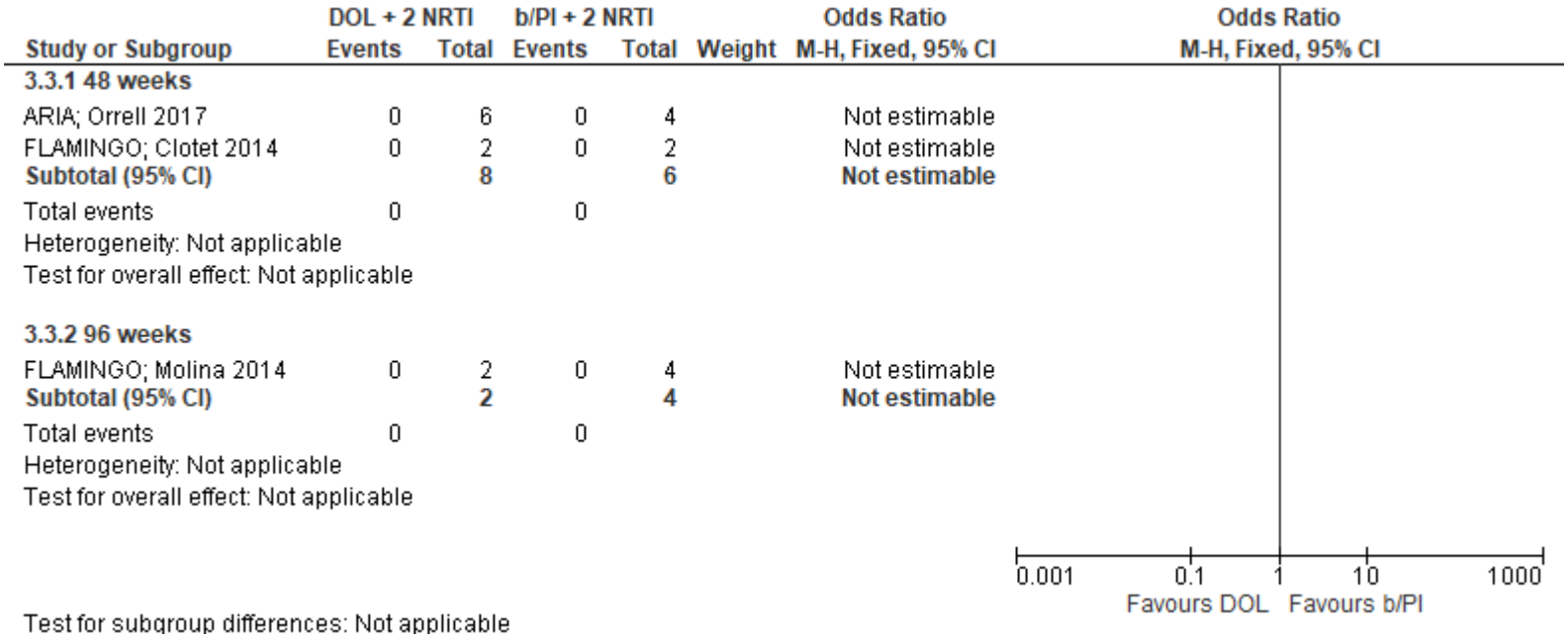


Figure 6. Success, failure and missing data at 96 weeks



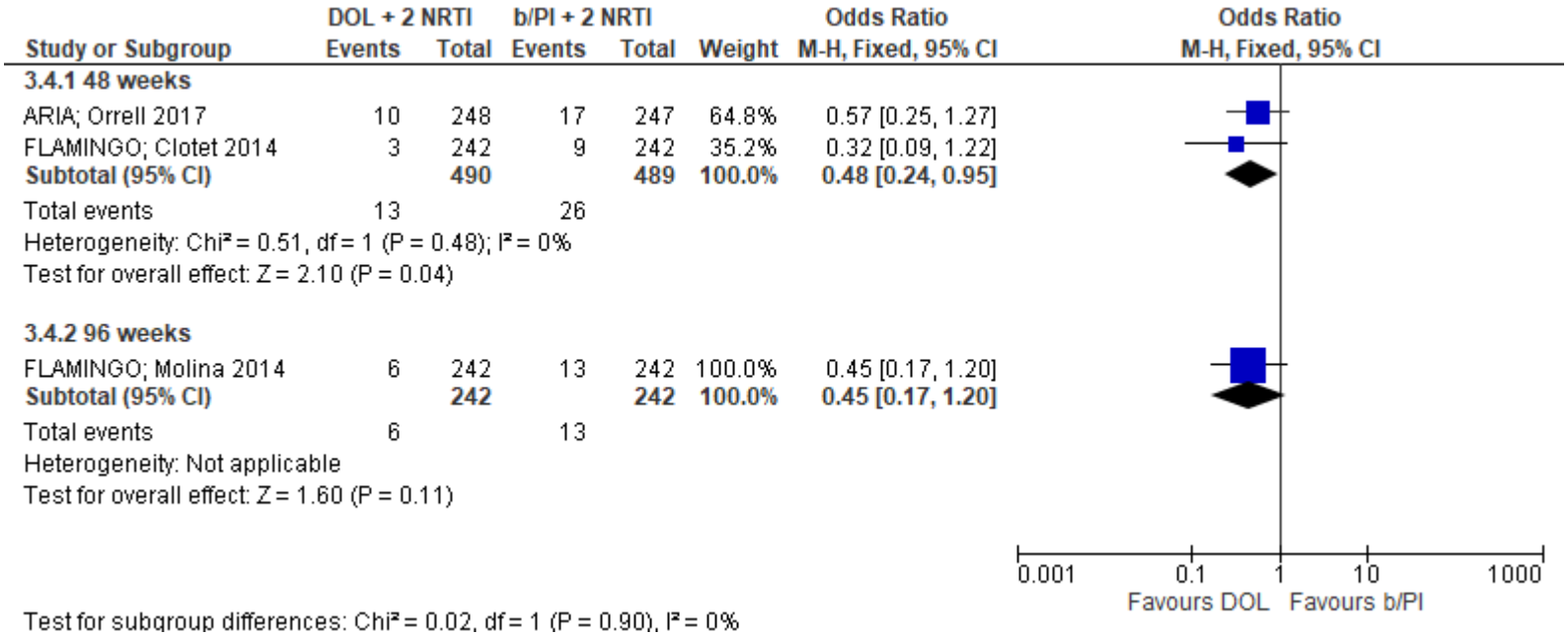
Failing with resistance

Forest plot of comparison: 3 DOL vs b/PI + any 2 NRTI, outcome: 3.3 Failure with resistance.



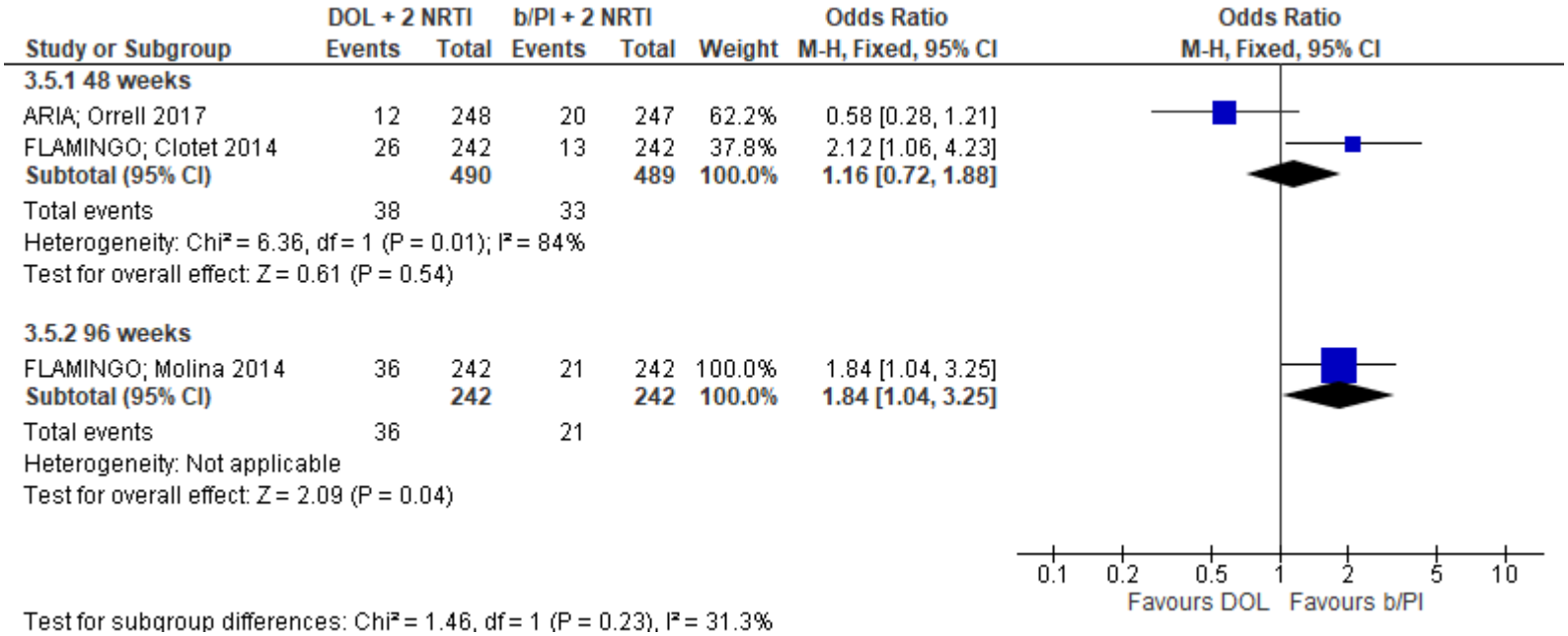
Adverse event (AE)-driven discontinuation

Forest plot of comparison: 3 DOL vs b/PI + any 2 NRTI, outcome: 3.4 AE-driven discontinuation.



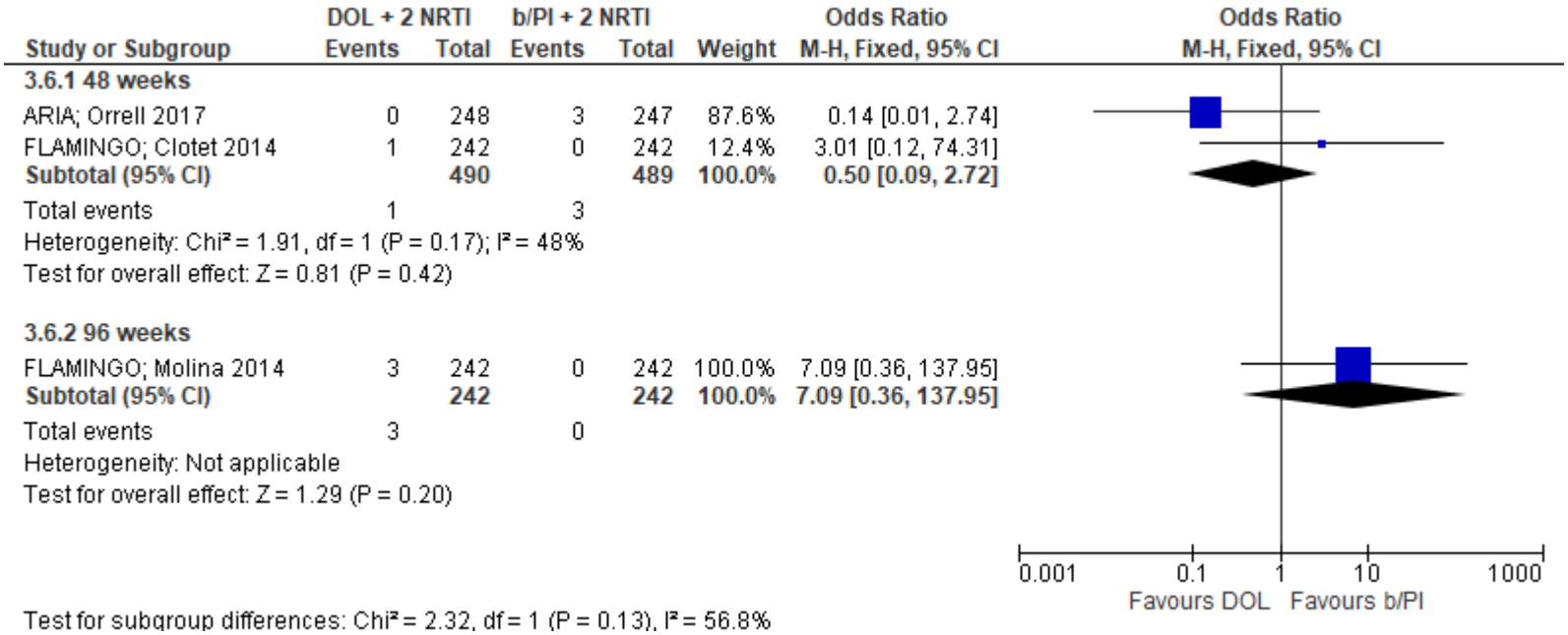
Serious adverse events

Forest plot of comparison: 3 DOL vs b/PI + any 2 NRTI, outcome: 3.5 Serious AE.



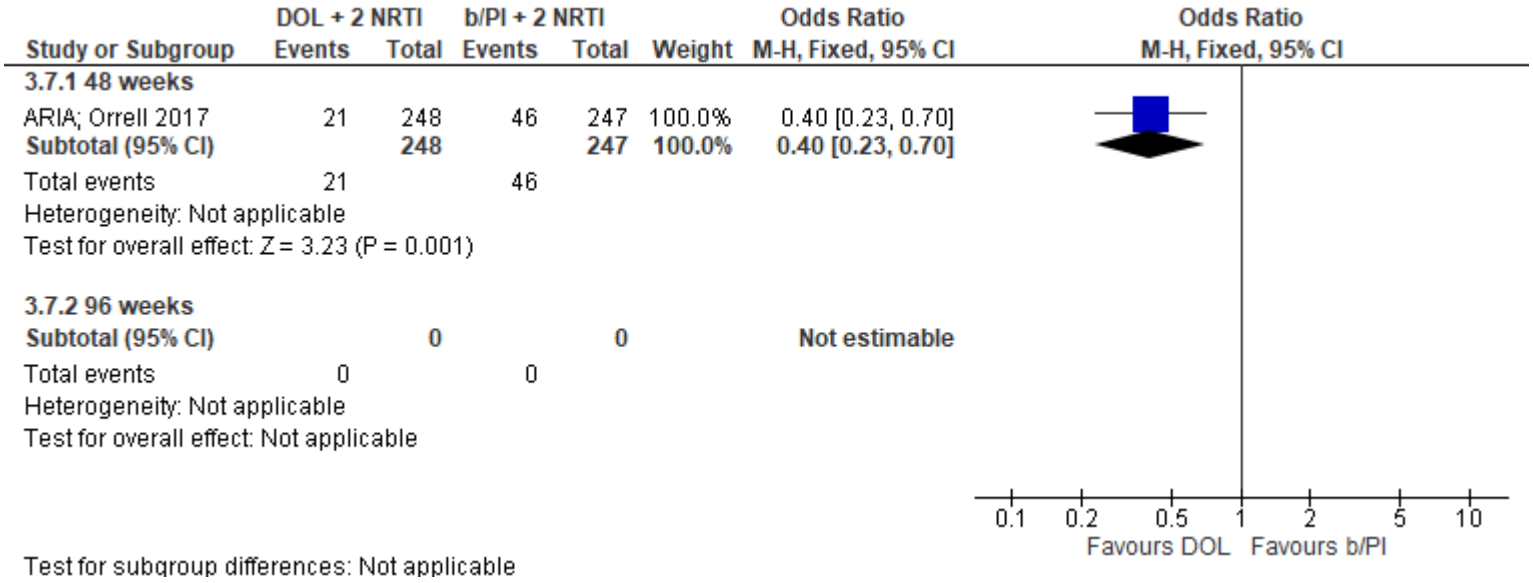
Drug-related SAE

Forest plot of comparison: 3 DOL vs b/PI + any 2 NRTI, outcome: 3.6 Drug-related serious AE.



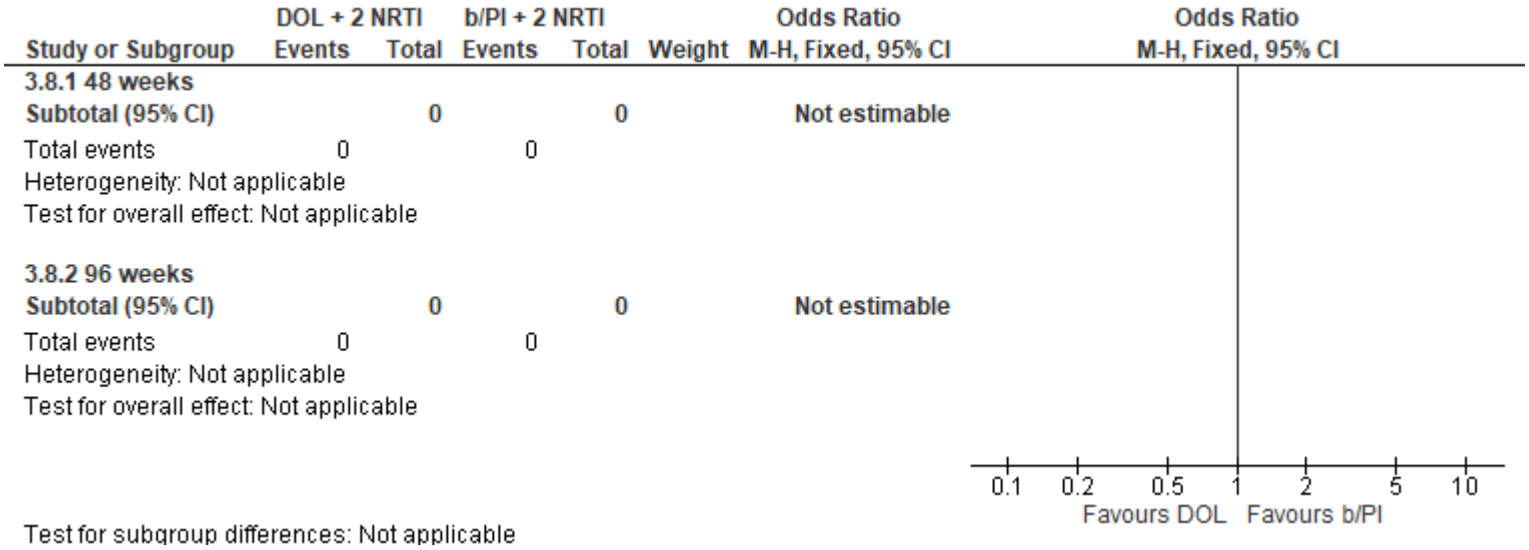
Grade 3/4 AE

Forest plot of comparison: 3 DOL vs b/PI + any 2 NRTI, outcome: 3.7 Grade 3/4 AE.



Drug-related Grade 3/4 AE

Forest plot of comparison: 3 DOL vs b/PI + any 2 NRTI, outcome: 3.8 Drug-related grade 3/4 AE.



GRADE table for critical outcomes

Outcomes	Anticipated absolute effects* (95% CI) Risk with b/PI + any 2 NRTI	Anticipated absolute effects* (95% CI) Risk with DOL	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Virological success - 48 weeks	769 per 1,000	**858 per 1,000** (813 to 894)	**OR 1.82** (1.31 to 2.54)	979 (2 RCTs)	⨁◯◯◯ Very low[a,b,c]	
Virological success - 96 weeks	678 per 1,000	**801 per 1,000** (728 to 860)	**OR 1.92** (1.27 to 2.91)	484 (1 RCT)	⨁◯◯◯ Very low[a,b]	
Virological failure - 48 weeks	108 per 1,000	**64 per 1,000** (41 to 97)	**OR 0.56** (0.35 to 0.88)	979 (2 RCTs)	⨁⨁◯◯ Low[b,c,d]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with b/PI + any 2 NRTI	Risk with DOL				
Virological failure - 96 weeks	116 per 1,000	**78 per 1,000** (44 to 136)	**OR 0.65** (0.35 to 1.20)	484 (1 RCT)	⨁◯◯◯ Very low[b,d,e]	[c]
Failure with resistance - 48 weeks	not pooled	not pooled	not pooled	14 (2 RCTs)	-	No events in either group
Failure with resistance - 96 weeks	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	6 (1 RCT)	-	No events in either group
AE-driven discontinuation - 48 weeks	53 per 1,000	**26 per 1,000** (13 to 51)	**OR 0.48** (0.24 to 0.95)	979 (2 RCTs)	⨁⨁◯◯ Low[b,c,d]	
AE-driven discontinuation - 96 weeks	54 per 1,000	**25 per 1,000** (10 to 64)	**OR 0.45** (0.17 to 1.20)	484 (1 RCT)	⨁◯◯◯ Very low[b,d,e]	
Serious AE - 48 weeks	67 per 1,000	**77 per 1,000** (50 to 120)	**OR 1.16** (0.72 to 1.88)	979 (2 RCTs)	⨁◯◯◯ Very low[b,c,d,e,f]	
Serious AE - 96 weeks	87 per 1,000	**149 per 1,000** (90 to 236)	**OR 1.84** (1.04 to 3.25)	484 (1 RCT)	⨁⨁◯◯ Low[b,d]	
Drug-related serious AE - 48 weeks	6 per 1,000	**3 per 1,000** (1 to 17)	**OR 0.50** (0.09 to 2.72)	979 (2 RCTs)	⨁◯◯◯ Very low[b,c,d,e]	
Drug-related serious AE - 96 weeks	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 7.09** (0.36 to 137.95)	484 (1 RCT)	⨁◯◯◯ Very low[b,d,e]	
Grade 3/4 AE - 48 weeks	186 per 1,000	**84 per 1,000** (50 to 138)	**OR 0.40** (0.23 to 0.70)	495 (1 RCT)	⨁⨁◯◯ Low[c,d]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with b/PI + any 2 NRTI	**Risk with DOL**				
Grade 3/4 AE - 96 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome
Drug-related grade 3/4 AE - 48 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome
Drug-related grade 3/4 AE - 96 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Difference between groups in numbers with missing data for virological outcomes

b. FLAMINGO: Low number of non-white, female, co-infected (HIV and hepatitis B or HIV and hepatitis C) patients or patients with advanced disease were enrolled

c. ARIA: women only.

d. Some concerns (open label study)

e. 95% Confidence interval spans 1

f. I^2 >60%

4 DOR vs b/PI + any 2 NRTI

NCT02275780 (DRIVE-FORWARD) data were published for week 48 results (Molina 2018) and week 96 results (Molina 2020).

Table 7. Key features of the included studies

Study name/ NCT number	Citation	Inclusion criteria	Exclusions	Population (n; demographics)	Intervention	Comparator	Outcomes
NCT02275780; DRIVE-FORWARD; MK-1439-018	Molina JM, Squires K, Sax PE, Cahn P, Lombaard J, DeJesus E, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. The lancet HIV. 2018;5(5):e211-e20.	Adults (aged ≥18 years) with HIV-1 infection who were naive to antiretroviral therapy, with plasma HIV-1 RNA at screening ≥1000 copies per mL, alkaline phosphatase concentrations ≤three times the upper limit of normal, aminotransferase concentrations ≤five times the upper limit of normal, a creatinine clearance rate of ≥50 mL/min at the time of screening, and no documented or	Uses or has had a recent history of using recreational or illicit drugs. Has been treated for a viral infection other than HIV-1, such as hepatitis B, with an agent that is active against HIV-1. Has documented or known resistance to study drugs including doravirine, darunavir, ritonavir, emtricitabine, tenofovir, abacavir and/or lamivudine. Has participated in a study with an investigational compound/device within the prior month, or	769 participants at 125 clinical centres in 15 countries (Argentina, Australia, Austria, Canada, Chile, Denmark, France, Germany, Italy, Romania, Russia, South Africa, Spain, UK, USA). The median age of the treated population was 33 years (IQR 27–42) and 760 (99%) participants were aged younger than	Doravirine with two investigator-selected NRTIs (tenofovir and emtricitabine or abacavir and lamivudine)	Darunavir plus ritonavir with two investigator-selected NRTIs (tenofovir and emtricitabine or abacavir and lamivudine)	The primary efficacy endpoint was the proportion of participants who had plasma HIV-1 RNA <50 copies per mL at week 48 as defined by the US FDA snapshot algorithm. Secondary endpoints were HIV-1 RNA <40 copies per mL and change from baseline in CD4 T-cell count. Exploratory endpoints were HIV-1 RNA <200 copies per

		known resistance to any of the study regimen components (defined broadly according to the presence of exclusionary mutations)	anticipates doing so during this study. Has used systemic immunosuppressive therapy or immune modulators within the prior 30 days, or anticipates doing so during this study. Has significant hypersensitivity or other contraindication to any of the components of the study drugs. Has a current (active) diagnosis of acute hepatitis due to any cause. Is pregnant, breastfeeding or expecting to conceive at any time during the study. Female who expects to donate eggs, or male who expects to donate sperm at any time during the study.	65 years. The treated population included 645 (84%) men and 121 (16%) women, of whom 560 (73%) were white, 73 (10%) had previously been diagnosed with AIDS (as reported by the investigator), and 538 (70%) had subtype B HIV-1 infection			mL, time to loss of virological response, protocol-defined virological failure (PDVF), and the development of viral resistance to the study medications. Safety outcomes were change from baseline in LDL-cholesterol and non-HDL-cholesterol, incidence of adverse events, time to discontinuation because of adverse events, and predefined limits of change in laboratory parameters.
	Molina, JM; Squires, K; Sax, PE; Cahn, P; Lombaard, J; DeJesus, E; Lai, MT; Rodgers, A; Lupinacci, L; Kumar, S; Sklar, P; Hanna, GJ; Hwang, C; Martin, EA.	As above	As above	As above	As above	As above	As above

	Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 96-week results of a randomised, double-blind, non-inferiority, phase 3 trial. The lancet. HIV 2020; 7(1): e16-e26. DOI: 10.1016/S2352-3018(19)30336-4. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02007909/full						

Table 8. Comparisons included in this section

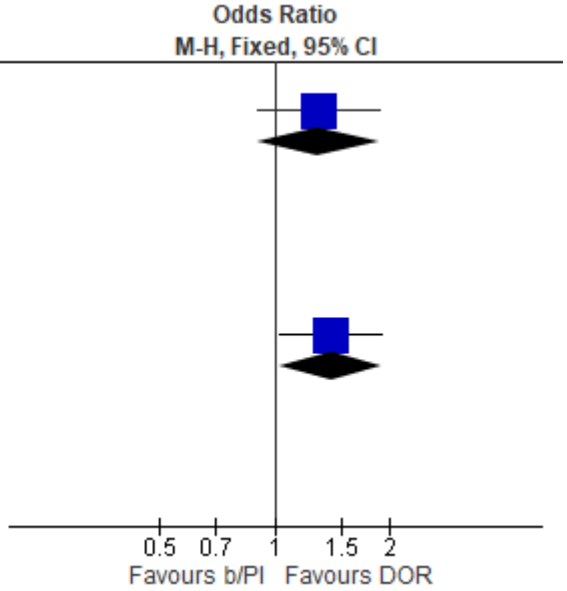
Study name/ NCT number	Intervention (2 NRTI + DOR)	Comparator (2 NRTI + b/PI)
NCT02275780; DRIVE-FORWARD; MK-1439-018	Doravirine with two investigator-selected NRTIs (tenofovir [DF] and emtricitabine or abacavir and lamivudine)	Darunavir plus ritonavir with two investigator-selected NRTIs (tenofovir [DF] and emtricitabine or abacavir and lamivudine)

Virological success, failure and missing data

Forest plot of comparison: 4 DOR vs b/PI + any 2 NRTI, outcome: 4.1 Virological success.

Study or Subgroup	DOR + 2 NRTI Events	Total	b/PI + 2 NRTI Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
4.1.1 48 weeks						
DRIVE-FORWARD; Molina 2018	321	383	306	383	100.0%	1.30 [0.90, 1.88]
Subtotal (95% CI)		**383**		**383**	**100.0%**	**1.30 [0.90, 1.88]**
Total events	321		306			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						
4.1.2 96 weeks						
DRIVE-FORWARD; Molina 2020	277	379	248	376	100.0%	1.40 [1.03, 1.91]
Subtotal (95% CI)		**379**		**376**	**100.0%**	**1.40 [1.03, 1.91]**
Total events	277		248			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.12 (P = 0.03)						

Test for subgroup differences: $Chi^2 = 0.09$, df = 1 (P = 0.77), $I^2 = 0\%$



Forest plot of comparison: 4 DOR vs b/PI + any 2 NRTI, outcome: 4.2 Virological failure.

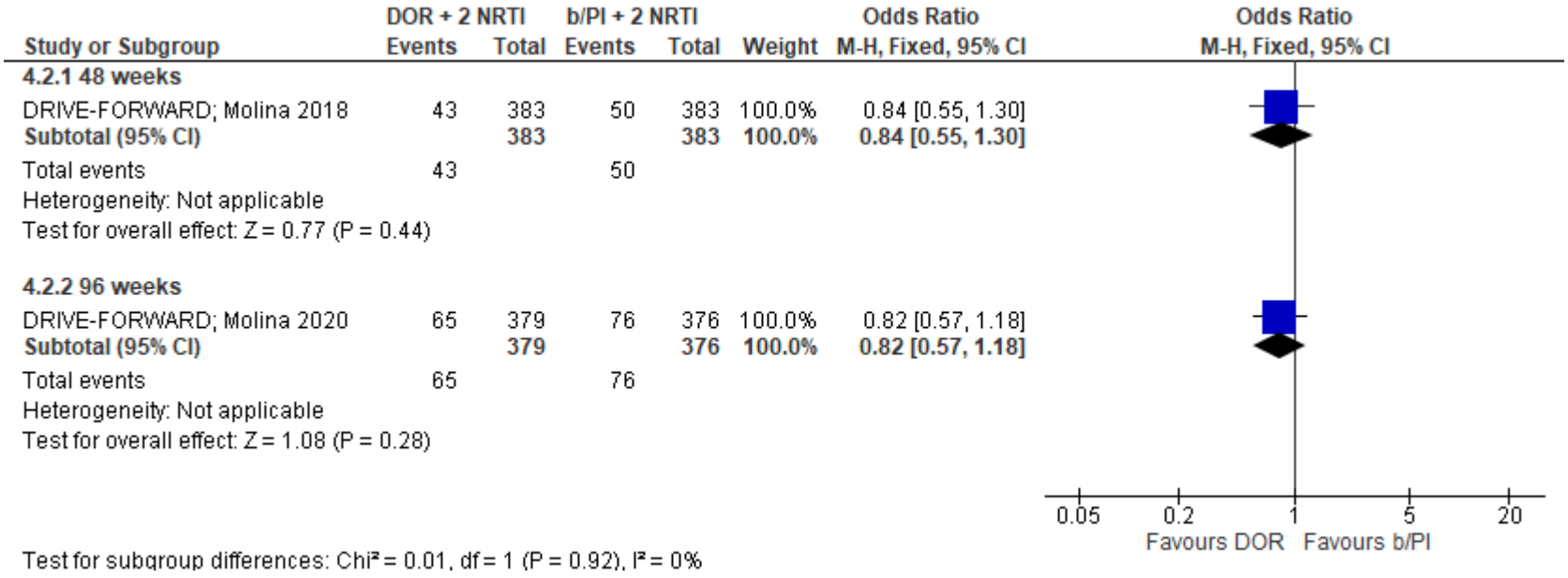


Figure 7. Success, failure and missing data at 48 weeks

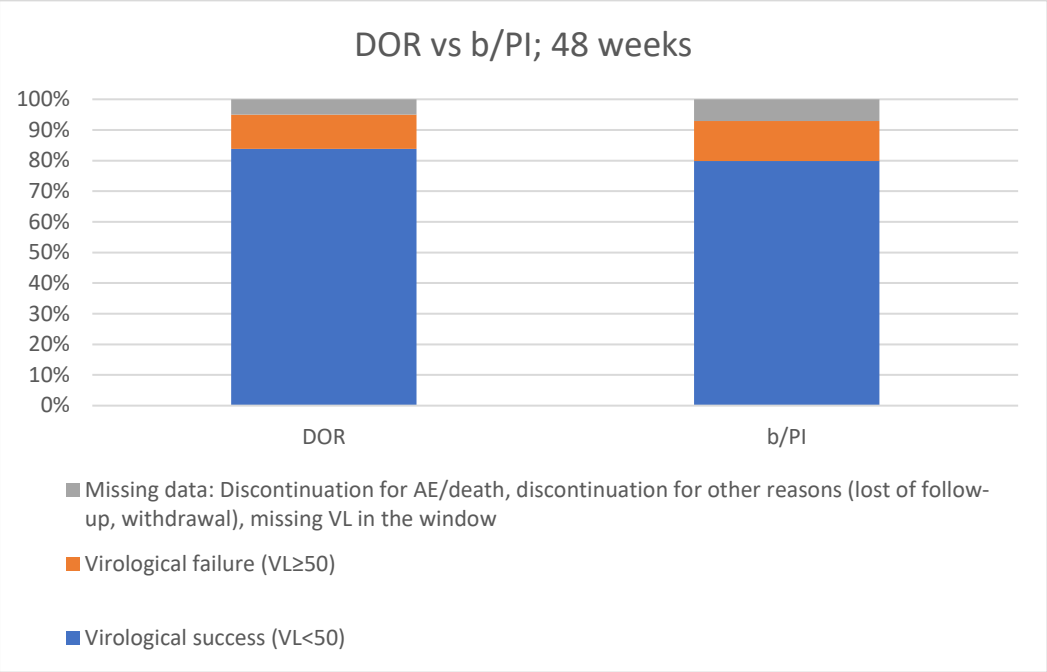
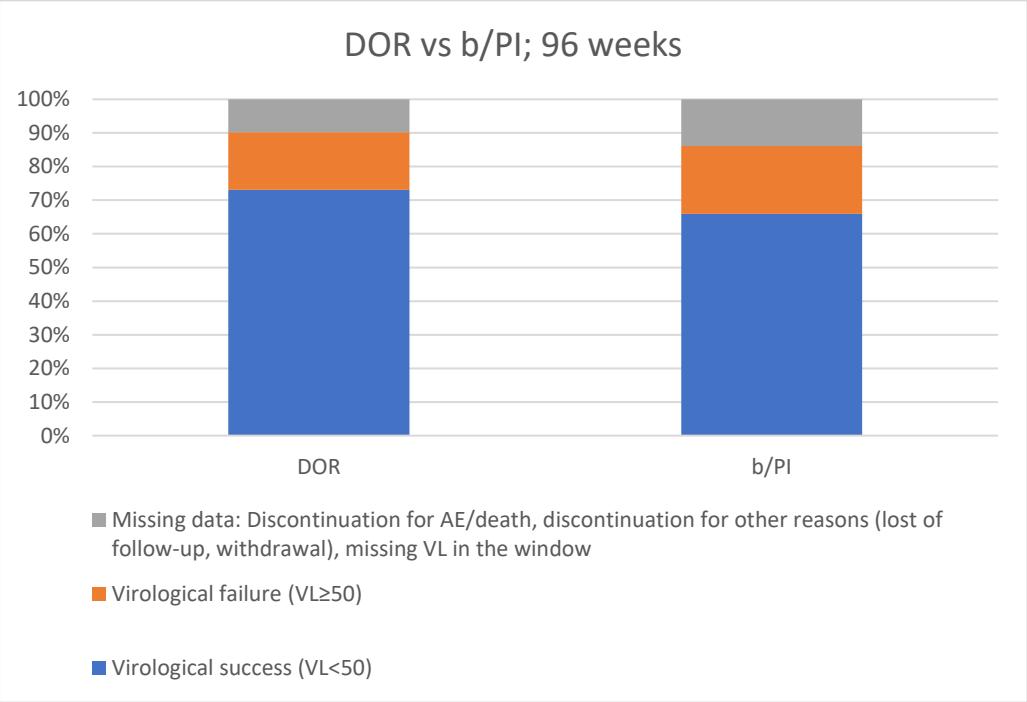
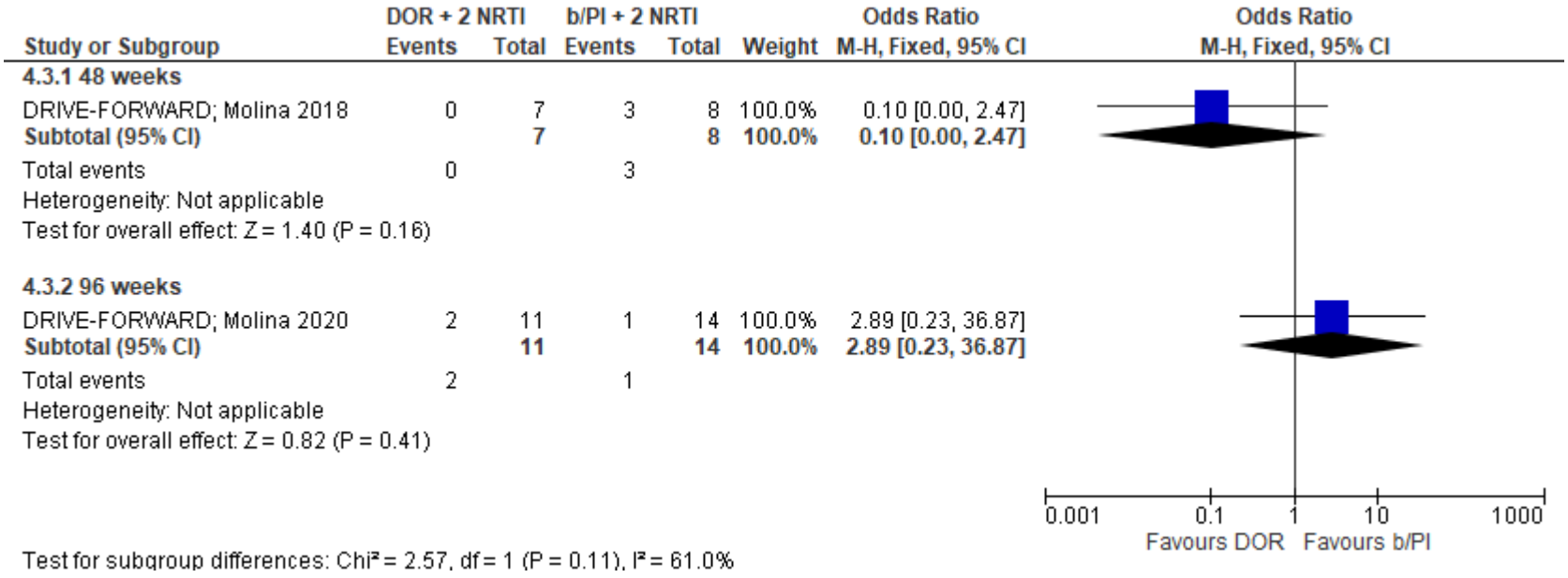


Figure 8. Success, failure and missing data at 96 weeks



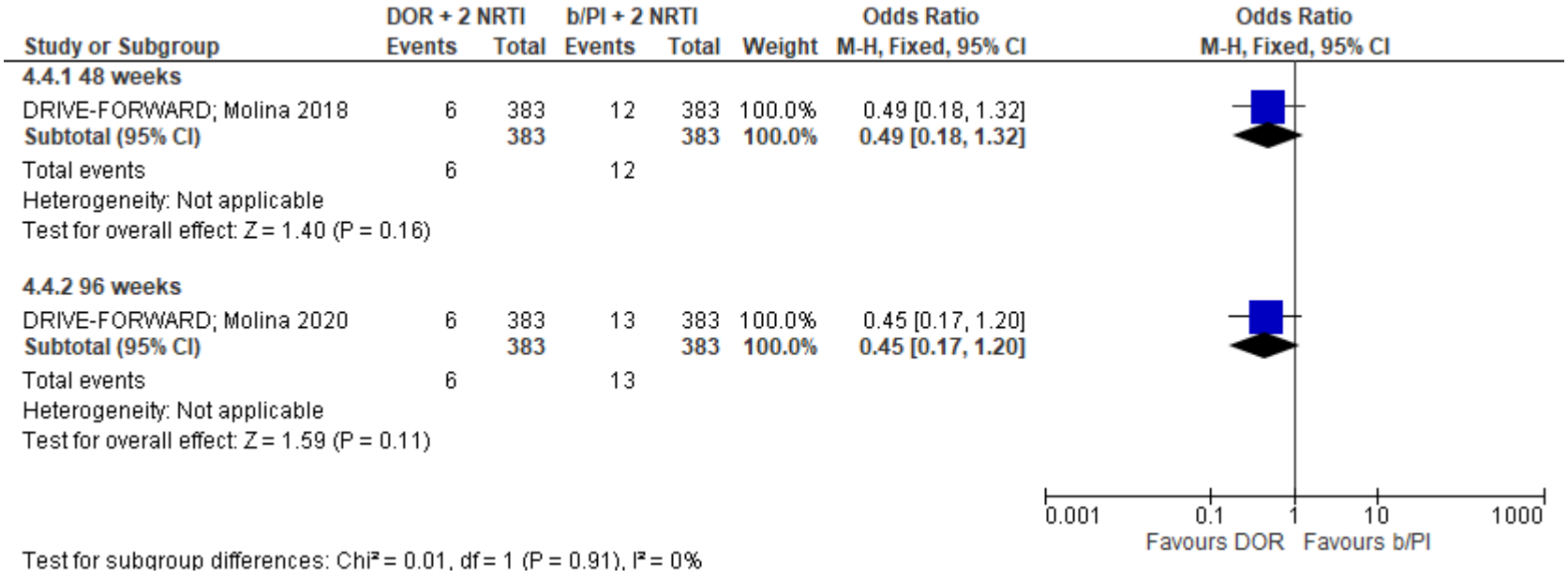
Failing with resistance

Forest plot of comparison: 4 DOR vs b/PI + any 2 NRTI, outcome: 4.3 Failure with resistance.



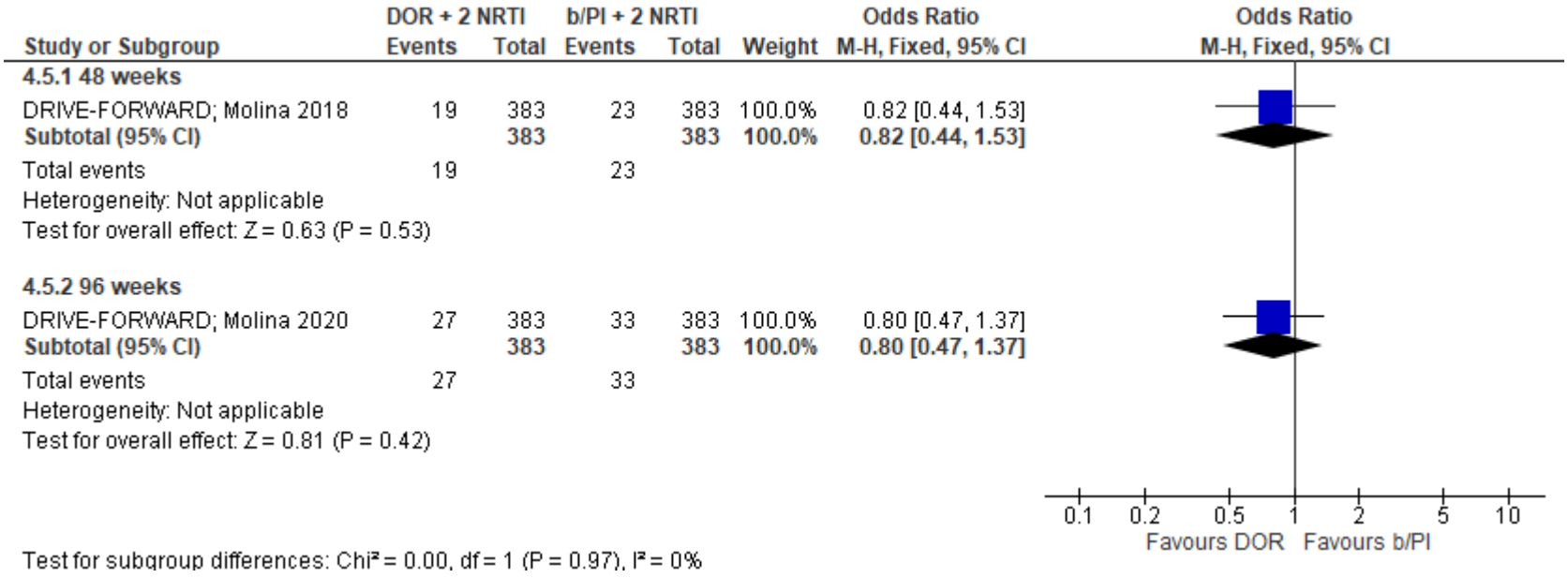
Adverse event (AE)-driven discontinuation

Forest plot of comparison: 4 DOR vs b/PI + any 2 NRTI, outcome: 4.4 AE-driven discontinuation.



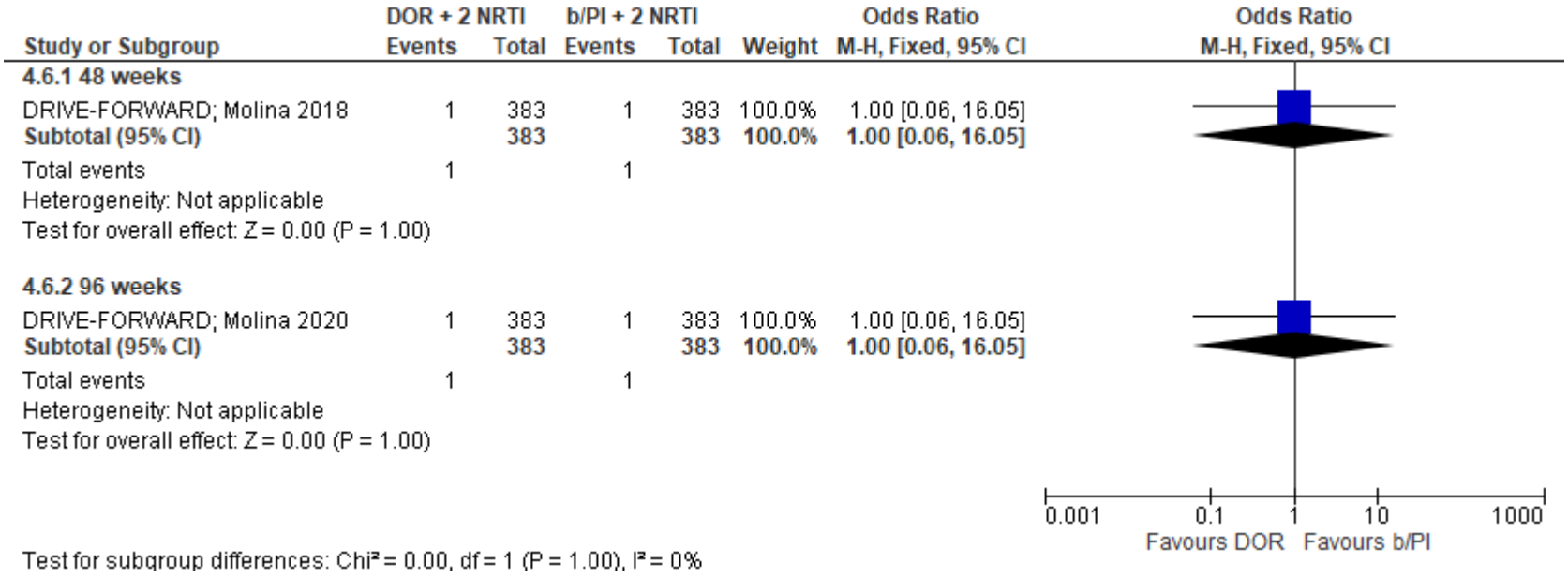
Serious adverse events

Forest plot of comparison: 4 DOR vs b/PI + any 2 NRTI, outcome: 4.5 Serious AE.



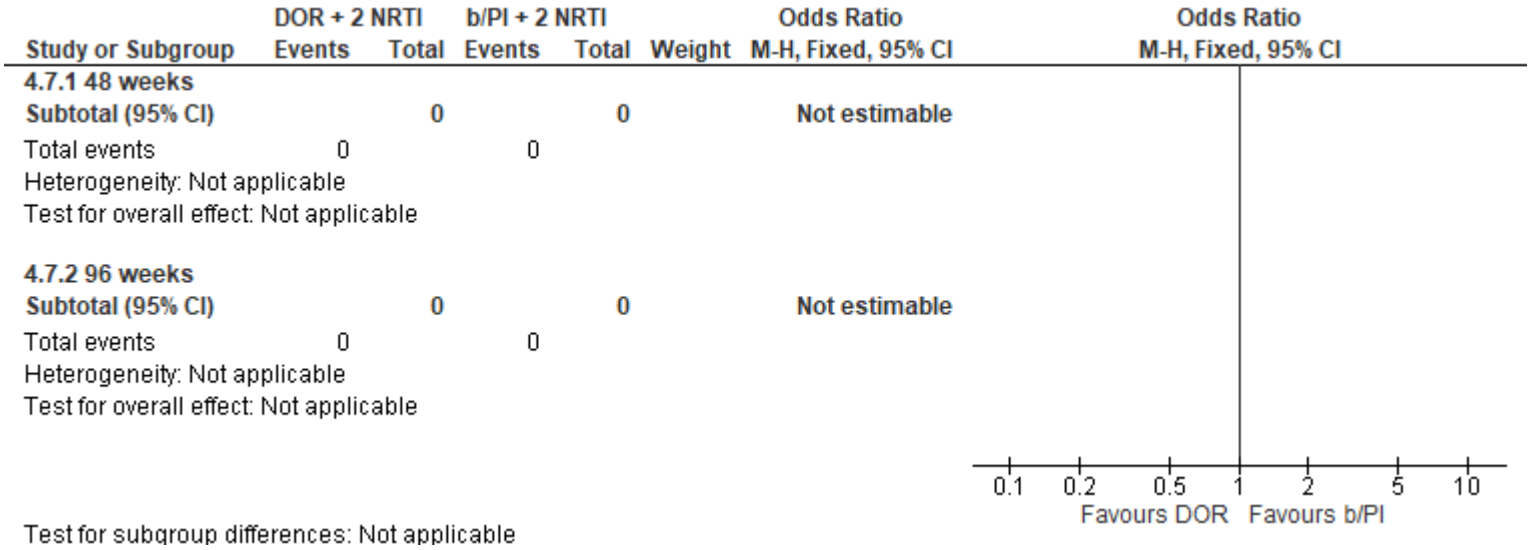
Drug-related SAE

Forest plot of comparison: 4 DOR vs b/PI + any 2 NRTI, outcome: 4.6 Drug-related serious AE.



Grade 3/4 AE

Forest plot of comparison: 4 DOR vs b/PI + any 2 NRTI, outcome: 4.7 Grade 3/4 AE.

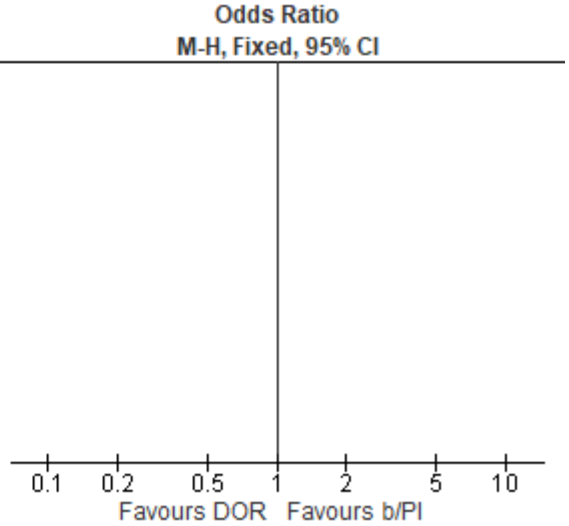


Drug-related Grade 3/4 AE

Forest plot of comparison: 4 DOR vs b/PI + any 2 NRTI, outcome: 4.8 Drug-related grade 3/4 AE.

Study or Subgroup	DOR + 2 NRTI Events	Total	b/PI + 2 NRTI Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
4.8.1 48 weeks						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.8.2 96 weeks						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

Test for subgroup differences: Not applicable



GRADE table for critical outcomes

Outcomes	Anticipated absolute effects* (95% CI) Risk with b/PI + any 2 NRTI	Risk with DOR	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Virological success - 48 weeks	799 per 1,000	**838 per 1,000** (781 to 882)	**OR 1.30** (0.90 to 1.88)	766 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Virological success - 96 weeks	660 per 1,000	**731 per 1,000** (666 to 787)	**OR 1.40** (1.03 to 1.91)	755 (1 RCT)	⨁⨁◯◯ Low[a,c]	
Virological failure - 48 weeks	131 per 1,000	**112 per 1,000** (76 to 163)	**OR 0.84** (0.55 to 1.30)	766 (1 RCT)	⨁⨁◯◯ Low[a,b]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with b/PI + any 2 NRTI	Risk with DOR				
Virological failure - 96 weeks	202 per 1,000	**172 per 1,000** (126 to 230)	**OR 0.82** (0.57 to 1.18)	755 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Failure with resistance - 48 weeks	375 per 1,000	**57 per 1,000** (0 to 597)	**OR 0.10** (0.00 to 2.47)	15 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Failure with resistance - 96 weeks	71 per 1,000	**182 per 1,000** (17 to 739)	**OR 2.89** (0.23 to 36.87)	25 (1 RCT)	⨁⨁◯◯ Low[a,b]	
AE-driven discontinuation - 48 weeks	31 per 1,000	**16 per 1,000** (6 to 41)	**OR 0.49** (0.18 to 1.32)	766 (1 RCT)	⨁⨁◯◯ Low[a,b]	
AE-driven discontinuation - 96 weeks	34 per 1,000	**16 per 1,000** (6 to 40)	**OR 0.45** (0.17 to 1.20)	766 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Serious AE - 48 weeks	60 per 1,000	**50 per 1,000** (27 to 89)	**OR 0.82** (0.44 to 1.53)	766 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Serious AE - 96 weeks	86 per 1,000	**70 per 1,000** (42 to 114)	**OR 0.80** (0.47 to 1.37)	766 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Drug-related serious AE - 48 weeks	3 per 1,000	**3 per 1,000** (0 to 40)	**OR 1.00** (0.06 to 16.05)	766 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Drug-related serious AE - 96 weeks	3 per 1,000	**3 per 1,000** (0 to 40)	**OR 1.00** (0.06 to 16.05)	766 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Grade 3/4 AE - 48 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with b/PI + any 2 NRTI	Risk with DOR				
Grade 3/4 AE - 96 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome
Drug-related grade 3/4 AE - 48 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome
Drug-related grade 3/4 AE - 96 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Molina 2018: low number of women (121 [16%]) and participants aged older than 65 years (1%) enrolled in the trial.

b. 95% Confidence interval spans 1

c. >10% missing data

5 DOR vs EFV + any 2 NRTI

NCT02403674 (DRIVE-AHEAD) data were published for week 48 results (Orkin 2019) and week 96 results (Orkin 2021).

Table 9. Key features of the included studies

Study name/ NCT number	Citation	Inclusion criteria	Exclusions	Population (n; demographics)	Intervention	Comparator	Outcomes
NCT02403674; DRIVE-AHEAD; MK-1439A Protocol 021	Orkin C, Squires KE, Molina J-M, Sax PE, Wong W-W, Sussmann O, et al. Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate is non-inferior to Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in treatment-naive adults with Human Immunodeficiency Virus-1 Infection: Week 48 Results of the DRIVE-AHEAD Trial. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2019;68(4):535-44.	Men and women ≥18 years of age with plasma HIV-1 RNA of ≥1000 copies/mL (within 45 days before study treatment) who were naive to antiretroviral therapy were eligible for the trial if they had no documented or known resistance to any of the study drugs and had calculated creatinine clearance of ≥50 mL/min.	Documented or known resistance to any study drug. Treatment for a viral infection other than HIV-1 (such as hepatitis B) with an agent that is active against HIV-1, including, but not limited to, adefovir, tenofovir, entecavir, emtricitabine, or lamivudine (unless treatment occurred prior to the diagnosis of HIV). Significant hypersensitivity or other contraindication to any of the components of the study drugs. Current (active) diagnosis of acute hepatitis due to any cause; evidence of decompensated liver disease; or liver cirrhosis and a Child-Pugh Class C	728 participants at 126 sites worldwide. Age (years), Median (range) 31.0 (18, 70) Male, n (%) 616 (85%) Race, n (%): White 347 (48%) Black or African American 135 (19%) Asian 124 (17%) Other (includes multiracial, American Indian, or Alaska Native) 122 (17%) Hispanic or Latino Ethnicity 246 (34%) CD4+ T-Cell Count: Median (range), cells/mm3: 397 (19, 1452) ≤200 cells/mm3, n	Doravirine/ lamivudine/ tenofovir disoproxil fumarate	Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate	The primary efficacy endpoint was the proportion of participants with <50 HIV-1 RNA copies/mL at week 48 (FDA snapshot approach; non-inferiority margin 10%). Secondary and exploratory efficacy endpoints included HIV-1 RNA of <40 copies/mL, HIV-1 RNA of <200 copies/mL, change from baseline in CD4+ T-cell counts, development of viral drug resistance and efficacy by subgroup.

			score or Pugh-Turcotte (CPT) score >9. Pregnancy, breastfeeding, or expecting to conceive. Use of recreational or illicit drugs, or recent history of drug or alcohol abuse or dependence.	(%): 90 (12%) >200 cells/mm3, n (%): 638 (88%) Plasma HIV-1 RNA: Median (range), log10 copies/mL 4.4 (2.4, 6.4) ≤100 000 copies/mL, n (%) 573 (79%) >100 000 copies/mL, n (%) 155 (21%) History of AIDS, n (%) 99 (14%) Hepatitis B and/or C (evidence of hepatitis B surface antigen or hepatitis C virus RNA), n (%) 20 (3%) HIV-1 Subtype B, n (%) 485 (67%)			
	Orkin C, Squires KE, Molina JM, Sax PE, Sussmann O, Lin G, Kumar S, Hanna GJ, Hwang C, Martin E, Teppler H. Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (TDF) versus Efavirenz/Emtricitabine/TDF in treatment-naive adults with Human Immunodeficiency Virus Type 1 infection: Week 96 results of the randomized, double-blind, Phase 3 DRIVE-AHEAD noninferiority trial. Clin Infect Dis. 2021 Jul 1;73(1):33-42. doi:	As above	As above	As above	As above	As above	As above

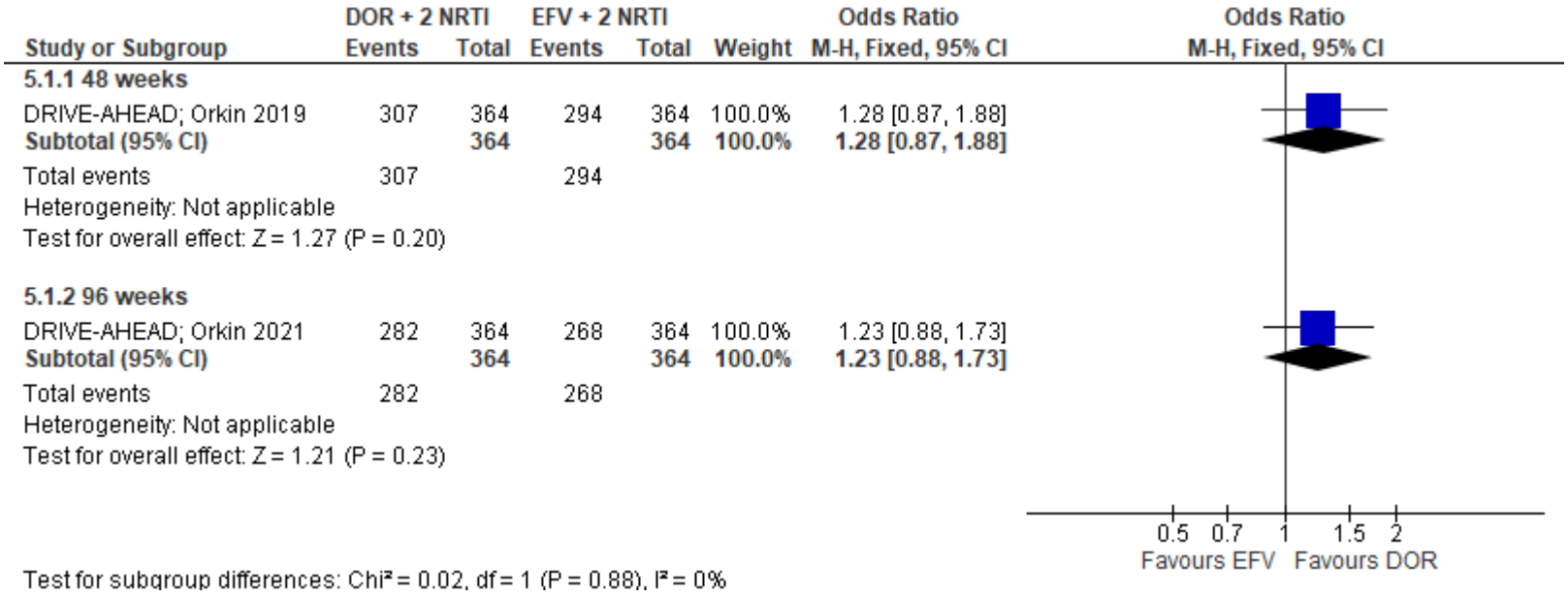
	10.1093/cid/ciaa822. PMID: 33336698; PMCID: PMC8246893.						

Table 10. Comparisons included in this section

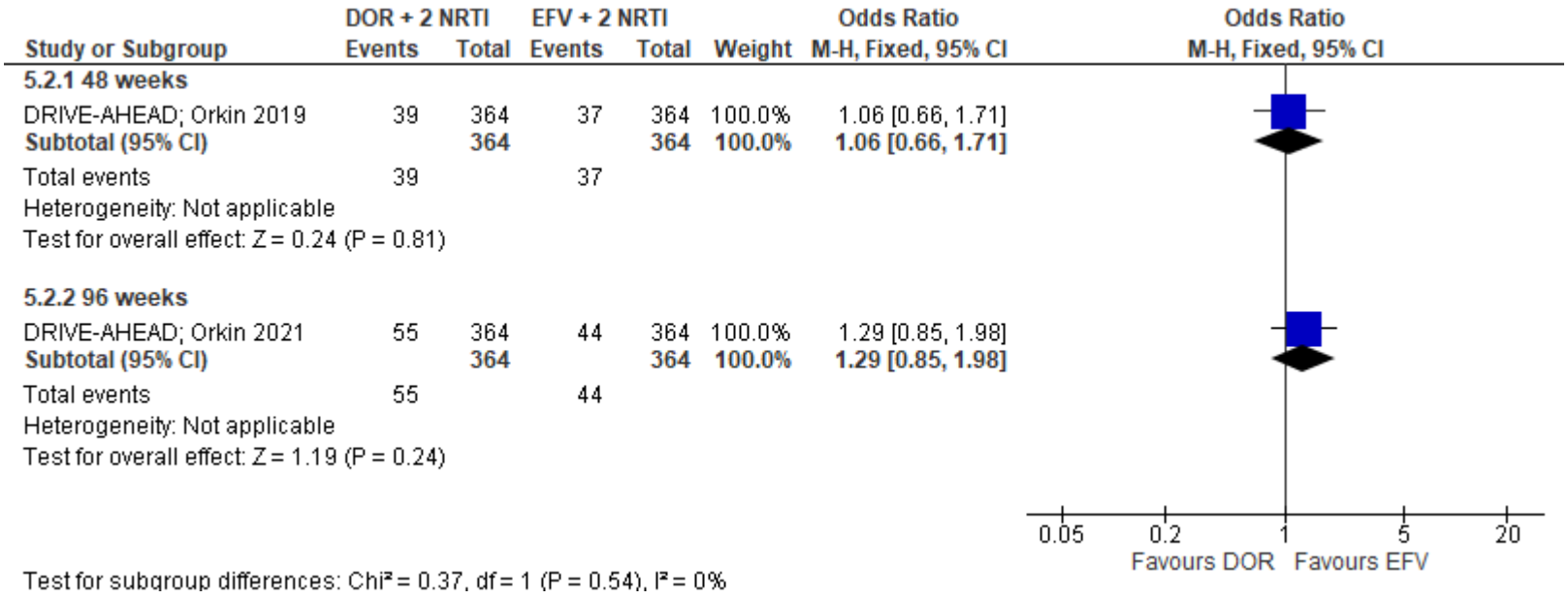
Study name/ NCT number	Intervention (2 NRTI + DOR)	Comparator (2 NRTI + EFV)
NCT02403674; DRIVE-AHEAD; MK-1439A Protocol 021	Doravirine, lamivudine and tenofovir disoproxil fumarate	Efavirenz, emtricitabine and tenofovir disoproxil fumarate

Virological success, failure and missing data

Forest plot of comparison: 5 DOR vs EFV + any 2 NRTI, outcome: 5.1 Virological success.



Forest plot of comparison: 5 DOR vs EFV + any 2 NRTI, outcome: 5.2 Virological failure.



The proportion of participants with missing data differed between groups as the rates of discontinuations for AEs differed between groups.

Figure 9. Success, failure and missing data at 48 weeks

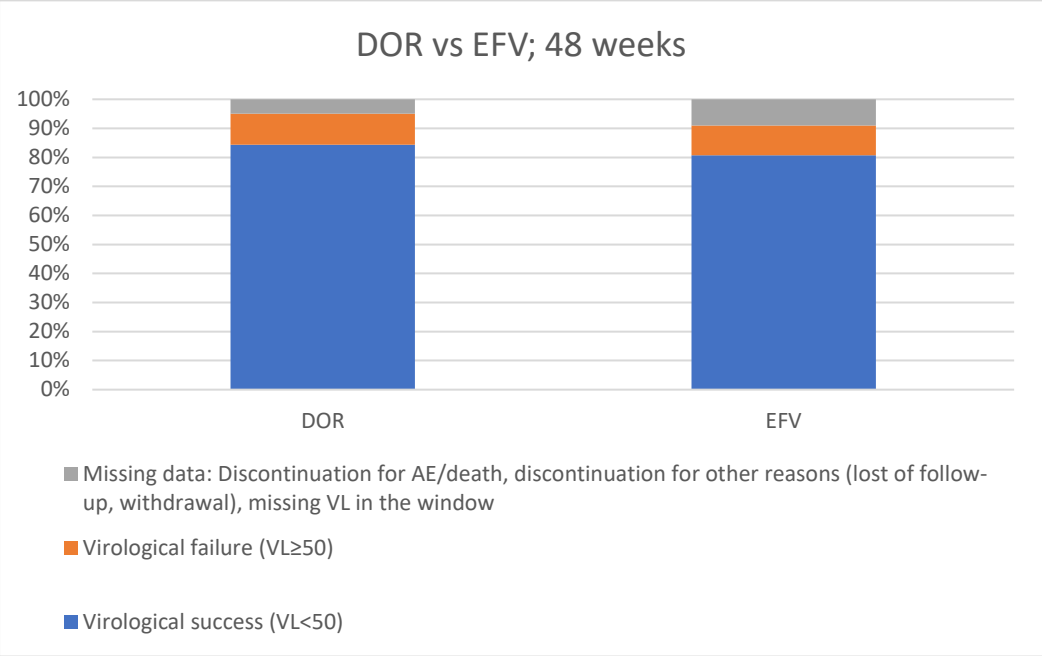
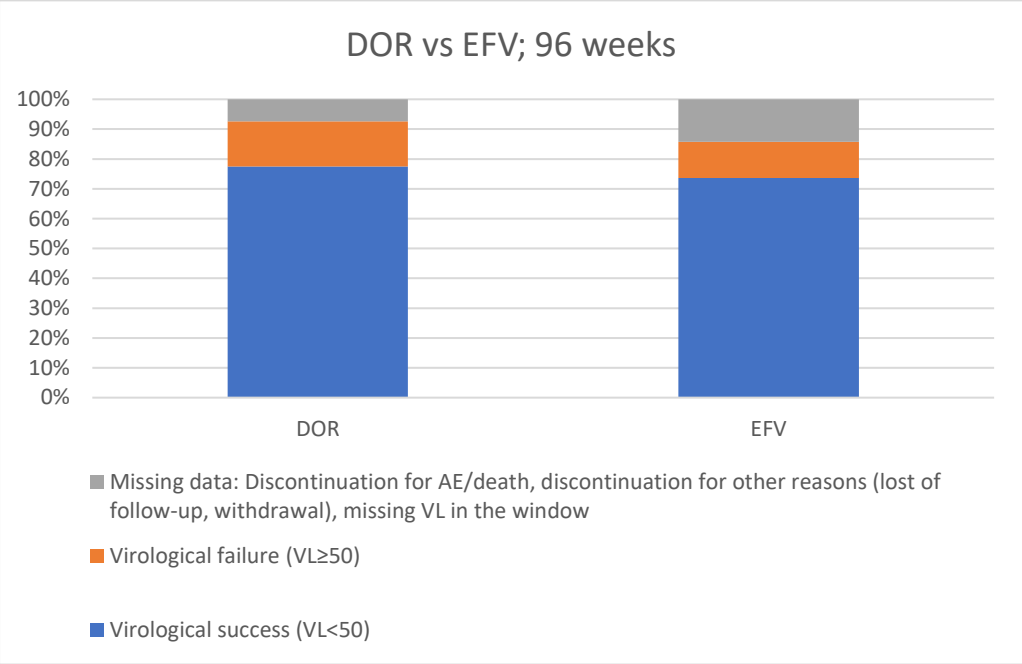
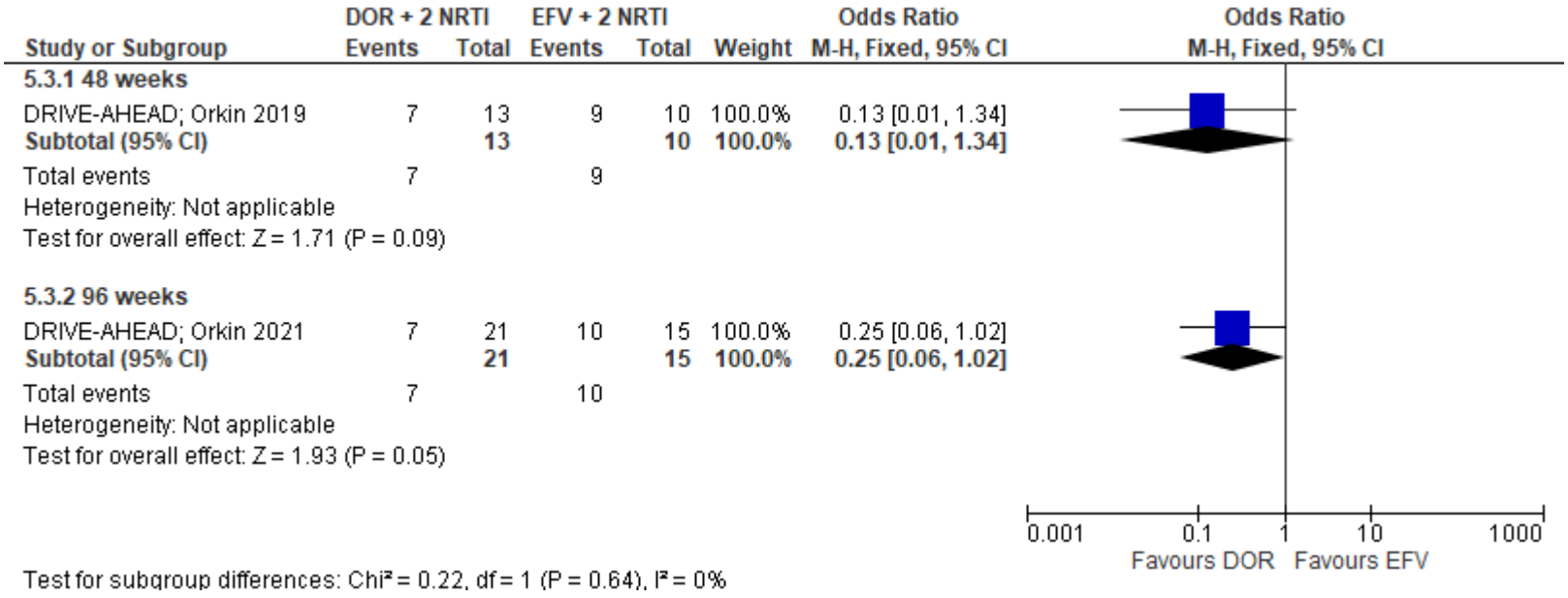


Figure 10. Success, failure and missing data at 96 weeks



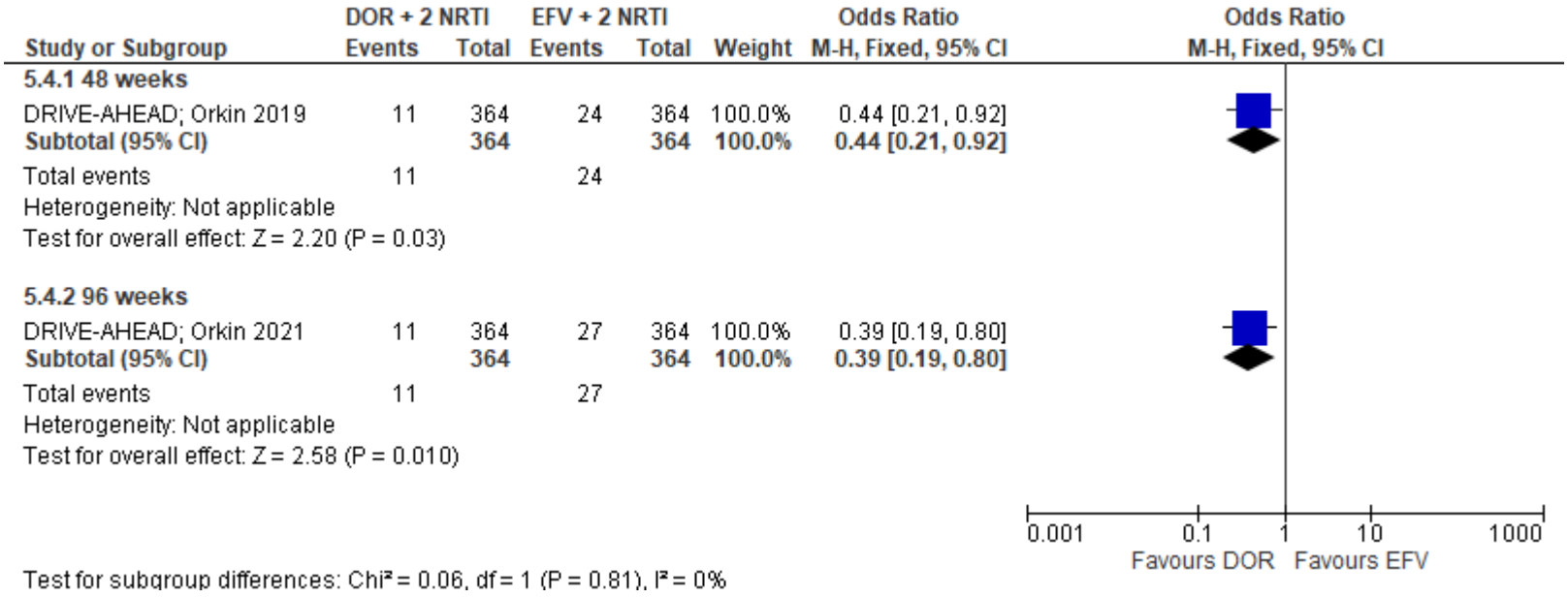
Failing with resistance

Forest plot of comparison: 5 DOR vs EFV + any 2 NRTI, outcome: 5.3 Failure with resistance.



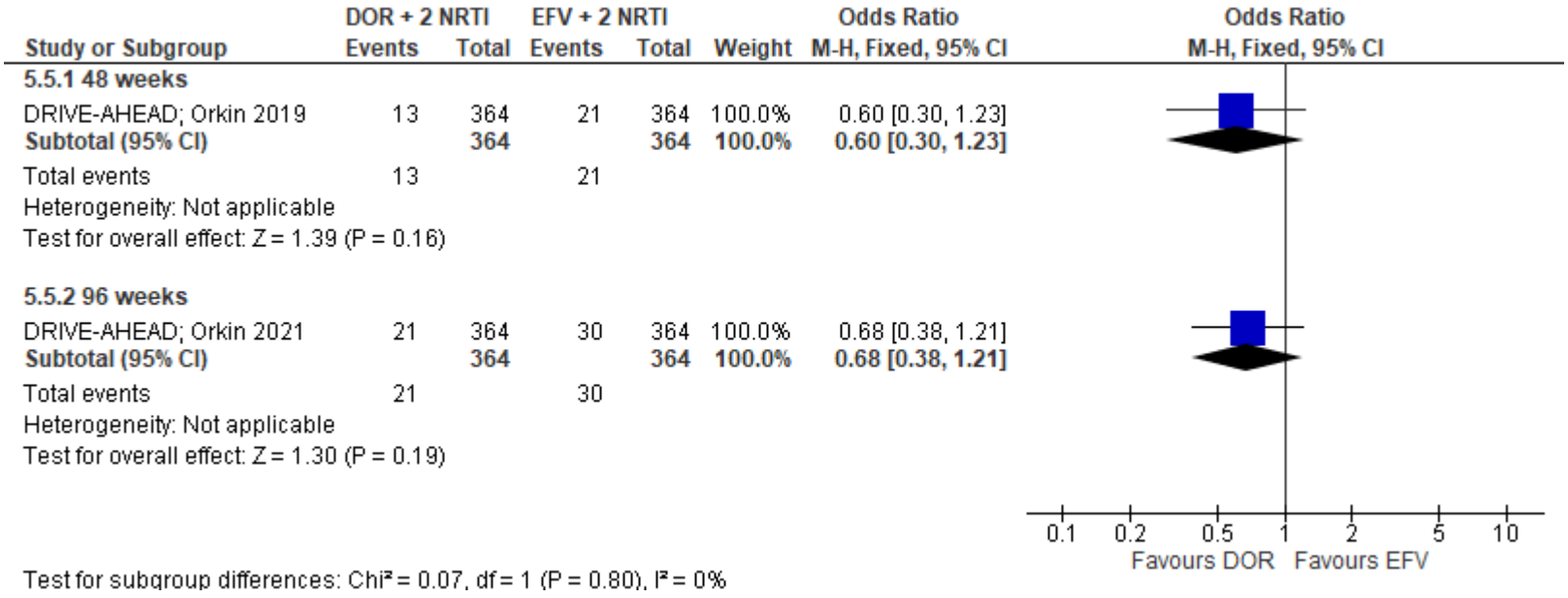
Adverse event (AE)-driven discontinuation

Forest plot of comparison: 5 DOR vs EFV + any 2 NRTI, outcome: 5.4 AE-driven discontinuation.



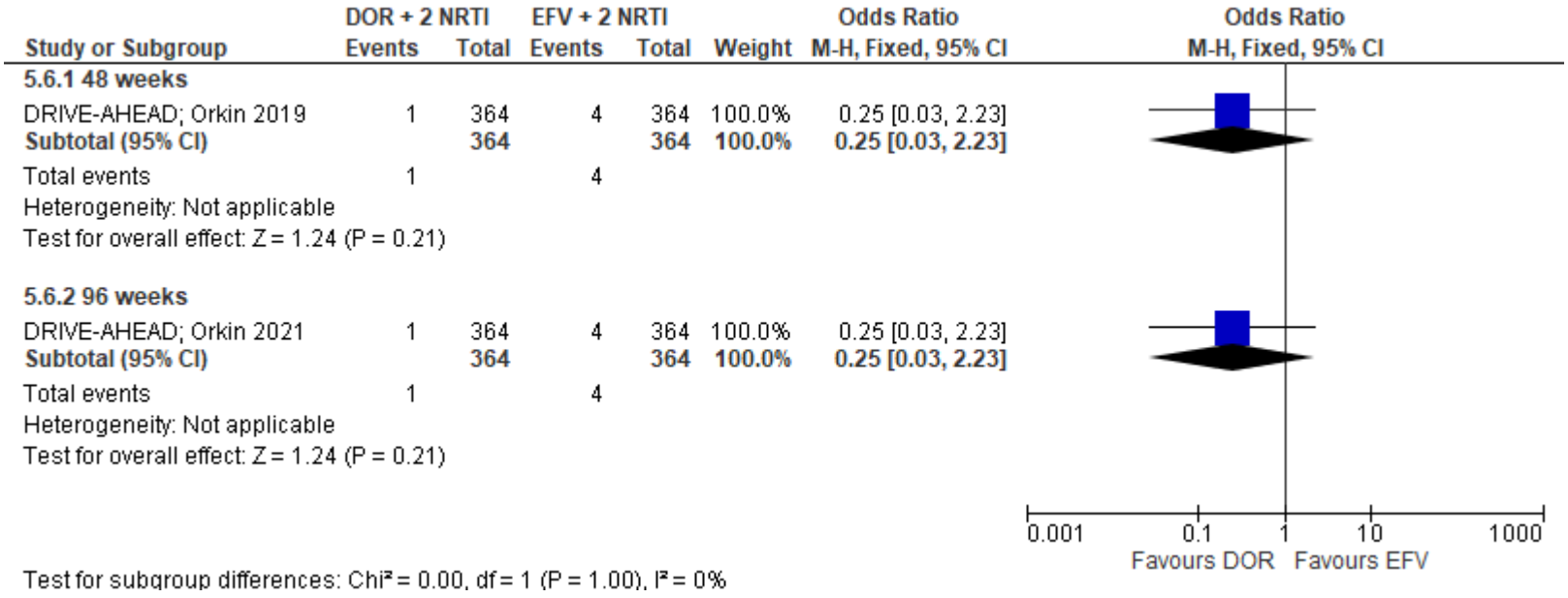
Serious adverse events

Forest plot of comparison: 5 DOR vs EFV + any 2 NRTI, outcome: 5.5 Serious AE.



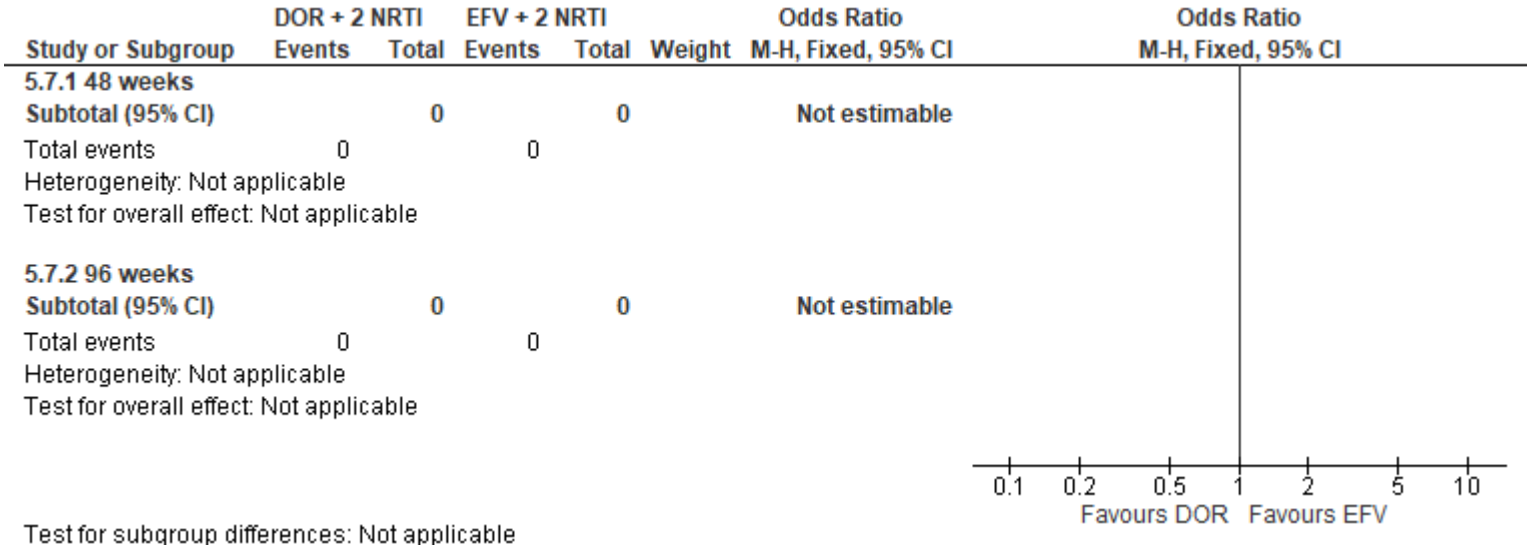
Drug-related SAE

Forest plot of comparison: 5 DOR vs EFV + any 2 NRTI, outcome: 5.6 Drug-related serious AE.



Grade 3/4 AE

Forest plot of comparison: 5 DOR vs EFV + any 2 NRTI, outcome: 5.7 Grade 3/4 AE.

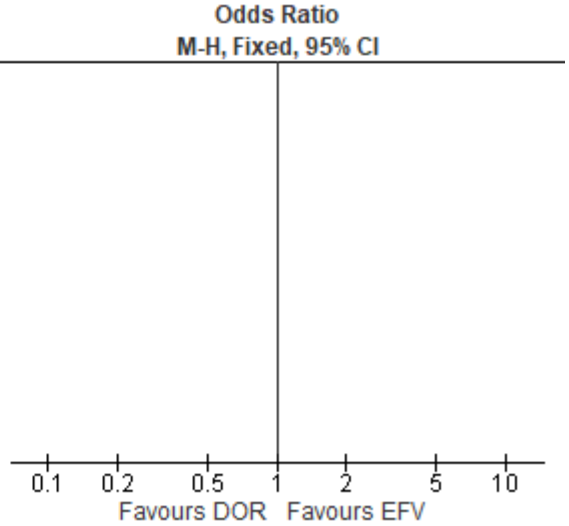


Drug-related Grade 3/4 AE

Forest plot of comparison: 5 DOR vs EFV + any 2 NRTI, outcome: 5.8 Drug-related grade 3/4 AE.

Study or Subgroup	DOR + 2 NRTI Events	Total	EFV + 2 NRTI Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
5.8.1 48 weeks						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
5.8.2 96 weeks						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

Test for subgroup differences: Not applicable



GRADE table for critical outcomes

Outcomes	Anticipated absolute effects* (95% CI) Risk with EFV + any 2 NRTI	Risk with DOR	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Virological success - 48 weeks	808 per 1,000	**843 per 1,000** (785 to 888)	**OR 1.28** (0.87 to 1.88)	728 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	
Virological success - 96 weeks	736 per 1,000	**774 per 1,000** (711 to 828)	**OR 1.23** (0.88 to 1.73)	728 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	
Virological failure - 48 weeks	102 per 1,000	**107 per 1,000** (69 to 162)	**OR 1.06** (0.66 to 1.71)	728 (1 RCT)	⨁⨁◯◯ Low[b,c]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with EFV + any 2 NRTI	**Risk with DOR**				
Virological failure - 96 weeks	121 per 1,000	**151 per 1,000** (105 to 214)	**OR 1.29** (0.85 to 1.98)	728 (1 RCT)	⨁⨁◯◯ Low[b,c]	
Failure with resistance - 48 weeks	900 per 1,000	**539 per 1,000** (83 to 923)	**OR 0.13** (0.01 to 1.34)	23 (1 RCT)	⨁⨁◯◯ Low[b,c]	
Failure with resistance - 96 weeks	667 per 1,000	**333 per 1,000** (107 to 671)	**OR 0.25** (0.06 to 1.02)	36 (1 RCT)	⨁⨁◯◯ Low[b,c]	
AE-driven discontinuation - 48 weeks	66 per 1,000	**30 per 1,000** (15 to 61)	**OR 0.44** (0.21 to 0.92)	728 (1 RCT)	⨁⨁⨁◯ Moderate[b]	
AE-driven discontinuation - 96 weeks	74 per 1,000	**30 per 1,000** (15 to 60)	**OR 0.39** (0.19 to 0.80)	728 (1 RCT)	⨁⨁⨁◯ Moderate[b]	
Serious AE - 48 weeks	58 per 1,000	**35 per 1,000** (18 to 70)	**OR 0.60** (0.30 to 1.23)	728 (1 RCT)	⨁⨁◯◯ Low[b,c]	
Serious AE - 96 weeks	82 per 1,000	**58 per 1,000** (33 to 98)	**OR 0.68** (0.38 to 1.21)	728 (1 RCT)	⨁⨁◯◯ Low[b,c]	
Drug-related serious AE - 48 weeks	11 per 1,000	**3 per 1,000** (0 to 24)	**OR 0.25** (0.03 to 2.23)	728 (1 RCT)	⨁⨁◯◯ Low[b,c]	
Drug-related serious AE - 96 weeks	11 per 1,000	**3 per 1,000** (0 to 24)	**OR 0.25** (0.03 to 2.23)	728 (1 RCT)	⨁⨁◯◯ Low[b,c]	
Grade 3/4 AE - 48 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with EFV + any 2 NRTI	Risk with DOR				
Grade 3/4 AE - 96 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome
Drug-related grade 3/4 AE - 48 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome
Drug-related grade 3/4 AE - 96 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Difference between groups in numbers with missing data for virological outcomes

b. Orkin 2019: Low numbers of women (15.4%), Blacks/African Americans (18.5%), and those with high baseline viral loads (>100000 copies/mL, 21.3%), low CD4+ T-cell counts (≤200/mm3, 12.4%), or hepatitis B/C co-infections (2.7%).

c. 95% Confidence interval spans 1

6 DOL/LAM vs TDF/FTC/DOL

GEMINI-1 and GEMINI-2 were identical in protocol (only undertaken in different study centres) and were published as pooled data; hereafter they are treated as a single trial (GEMINI-1/2) with all data pooled. GEMINI-1/2 data were published for week 48 (Cahn 2019) and week 96 (Cahn 2020).

Table 11. Key features of the included studies

Study name/ NCT number	Citation	Inclusion criteria	Exclusions	Population (n; demographics)	Intervention	Comparator	Outcomes
NCT02831673 (GEMINI-1) and NCT02831764 (GEMINI-2)	Cahn P, Madero JS, Arribas JR, Antinori A, Ortiz R, Clarke AE, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet. 2019;393(10167):143-55.	≥18 years with HIV-1 infection and naive to ART (≤10 days previous therapy with any ART). Entry criteria at study start specified screening viral loads of 1000-100 000 copies per mL but, as permitted per protocol, the upper limit was increased to 500 000 copies per mL during the study after an independent review of data from independently sponsored	Pre-existing major viral resistance mutations to NRTIs NNRTIs or PIs; and active US CDC stage 3 HIV disease, except for cutaneous Kaposi's sarcoma and CD4+ cell counts < 200 cells per µL.	1441 participants at 192 centres in 21 countries. Participants had a median age of 33 years (range 18–72), with most participants being younger than 50 years (1288 [90%] of 1433), men (1222 [85%]), and white (977 [68%]). Baseline HIV-1 RNA of more than 100 000 copies per mL occurred in 293 (20%) and CD4+ cell count of 200 cells per µL or less occurred	Dolutegravir plus lamivudine	Dolutegravir plus tenofovir disoproxil fumarate and emtricitabine	The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies per mL at week 48 using the FDA Snapshot algorithm. Secondary endpoints included proportion of participants with HIV-1 RNA <50 copies per mL at week 24, time to achieve HIV-1 RNA <50 copies per mL,

		studies evaluating the two-drug regimen of dolutegravir plus lamivudine. The study included women of reproductive potential if they were not pregnant or lactating and were using approved contraception.		in 118 (8%) participants.			absolute values and change from baseline to week 48 in CD4+ cell count, disease progression (i.e., HIV-associated conditions, AIDS, or death), and incidence of emergence of mutations conferring genotypic and phenotypic resistance to dolutegravir plus lamivudine or tenofovir disoproxil fumarate and emtricitabine in participants meeting criteria for confirmed virological withdrawal.
	Cahn, P; Madero, JS; Arribas, JR; Antinori, A; Ortiz, R; Clarke, AE; Hung, CC; Rockstroh, JK; Girard, PM; Sievers, J; Man, CY; Urbaityte, R; Brandon, DJ; Underwood, M; Tenorio, AR;	As above	As above	As above	As above	As above	As above

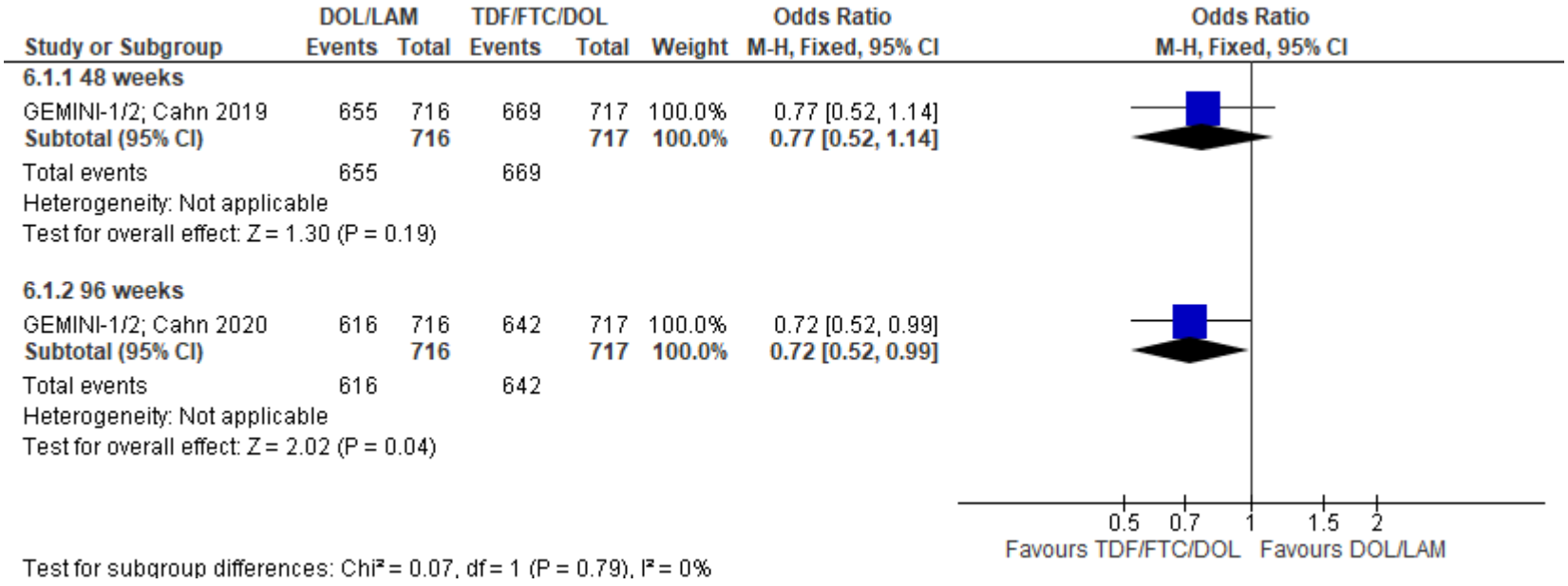
	Pappa, KA; Wynne, B; Gartland, M; Aboud, M; van Wyk, J; Smith, KY. Durable Efficacy of Dolutegravir Plus Lamivudine in Antiretroviral Treatment-Naive Adults With HIV-1 Infection: 96-Week Results From the GEMINI-1 and GEMINI-2 Randomized Clinical Trials. Journal of acquired immune deficiency syndromes (1999) 2020; 83(3): 310-318. DOI: 10.1097/QAI.0000000000002275. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02093396/full						

Table 12. Comparisons included in this section

Study name/ NCT number	Intervention (DOL/LAM)	Comparator (TDF/FTC/DOL)
NCT02831673 (GEMINI-1) and NCT02831764 (GEMINI-2)	Dolutegravir plus lamivudine	Dolutegravir plus tenofovir disoproxil fumarate and emtricitabine

Virological success, failure and missing data

Forest plot of comparison: 6 DOL/LAM vs TDF/FTC/DOL, outcome: 6.1 Virological success.



Forest plot of comparison: 6 DOL/LAM vs TDF/FTC/DOL, outcome: 6.2 Virological failure.

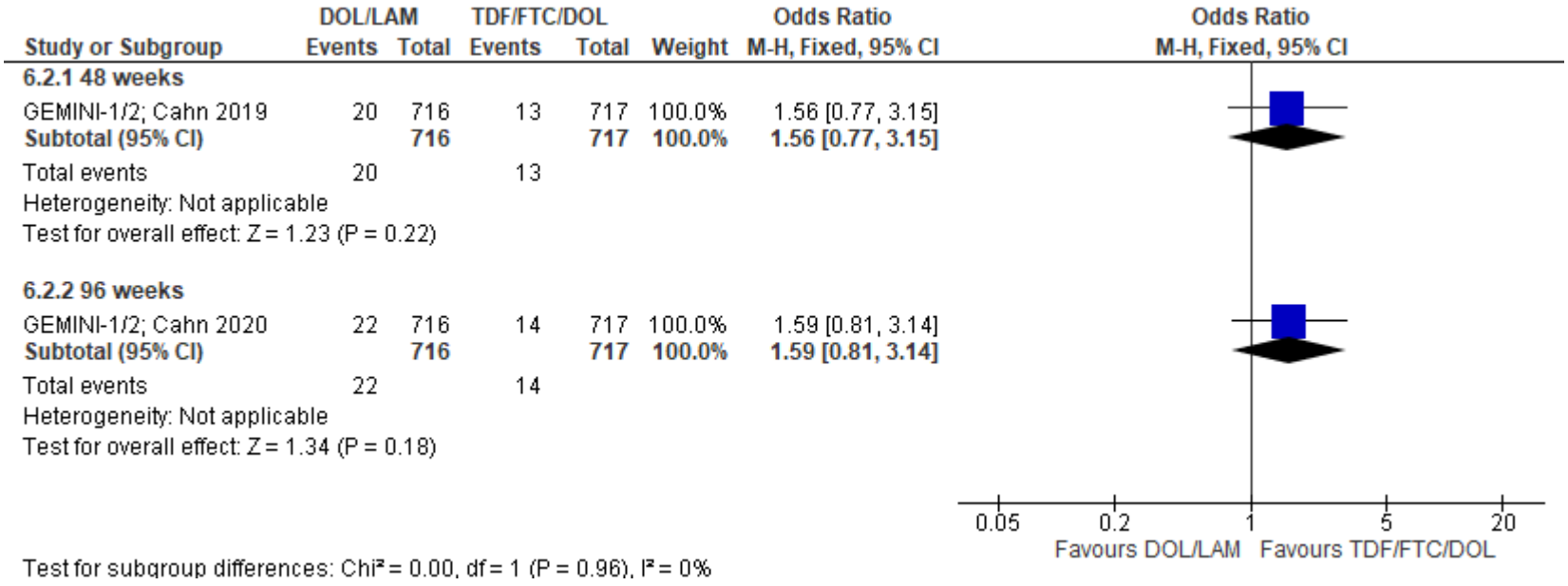


Figure 11. Success, failure and missing data at 48 weeks

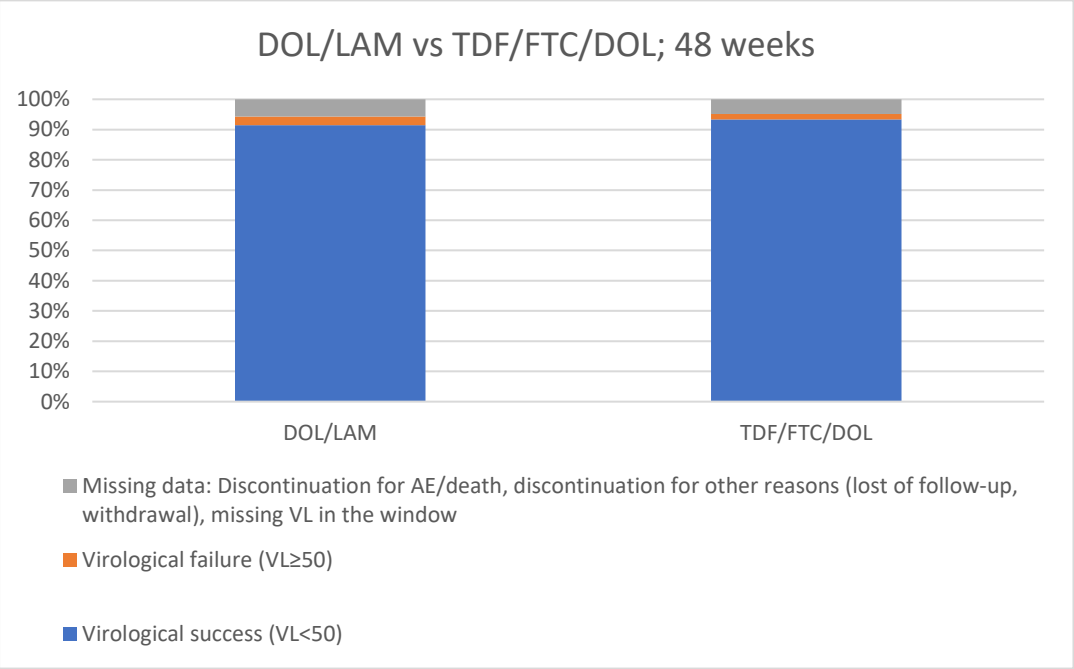
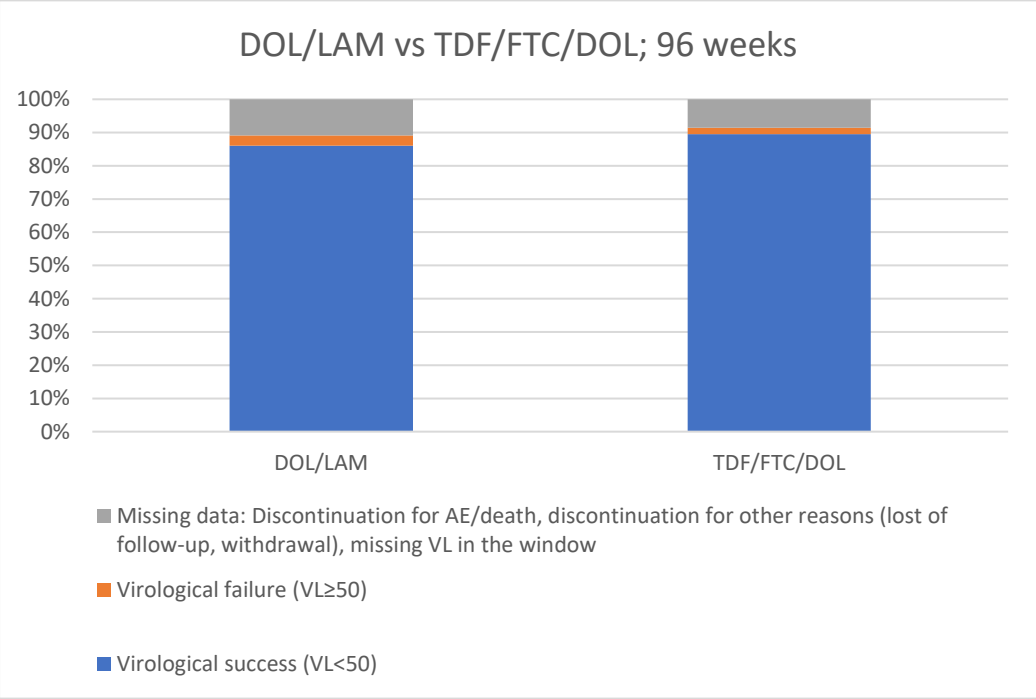


Figure 12. Success, failure and missing data at 96 weeks

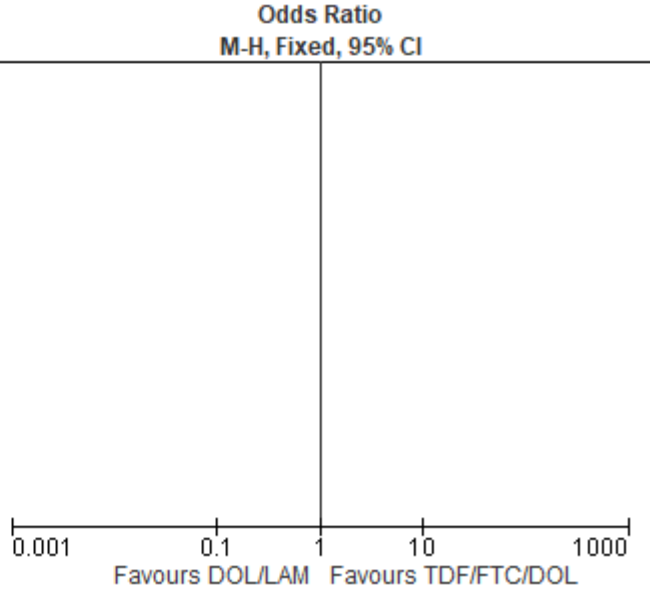


Failing with resistance

Forest plot of comparison: 6 DOL/LAM vs TDF/FTC/DOL, outcome: 6.3 Failure with resistance.

Study or Subgroup	DOL/LAM Events	DOL/LAM Total	TDF/FTC/DOL Events	TDF/FTC/DOL Total	Weight	Odds Ratio M-H, Fixed, 95% CI
6.3.1 48 weeks						
GEMINI-1/2; Cahn 2019	0	6	0	4		Not estimable
Subtotal (95% CI)		**6**		**4**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.3.2 96 weeks						
GEMINI-1/2; Cahn 2020	0	11	0	7		Not estimable
Subtotal (95% CI)		**11**		**7**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

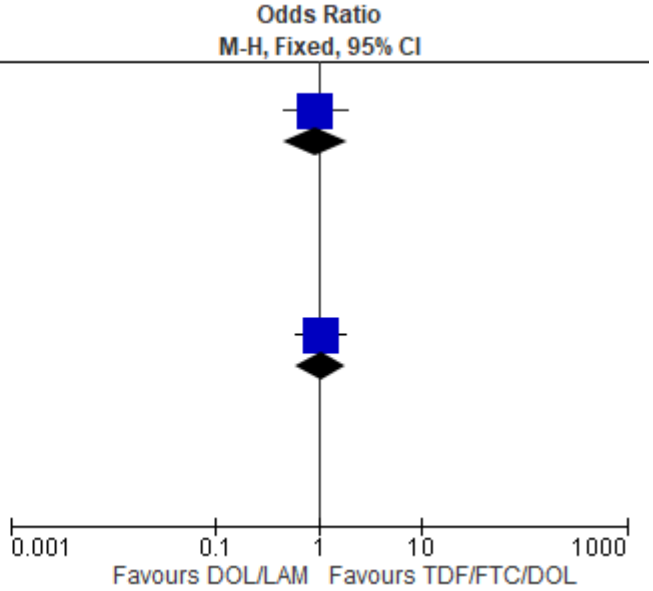
Test for subgroup differences: Not applicable



Adverse event (AE)-driven discontinuation

Forest plot of comparison: 6 DOL/LAM vs TDF/FTC/DOL, outcome: 6.4 AE-driven discontinuation.

Study or Subgroup	DOL/LAM Events	DOL/LAM Total	TDF/FTC/DOL Events	TDF/FTC/DOL Total	Weight	Odds Ratio M-H, Fixed, 95% CI
6.4.1 48 weeks						
GEMINI-1/2; Cahn 2019	15	716	16	717	100.0%	0.94 [0.46, 1.91]
Subtotal (95% CI)		**716**		**717**	**100.0%**	**0.94 [0.46, 1.91]**
Total events	15		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.18 (P = 0.86)						
6.4.2 96 weeks						
GEMINI-1/2; Cahn 2020	24	716	23	717	100.0%	1.05 [0.59, 1.87]
Subtotal (95% CI)		**716**		**717**	**100.0%**	**1.05 [0.59, 1.87]**
Total events	24		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						



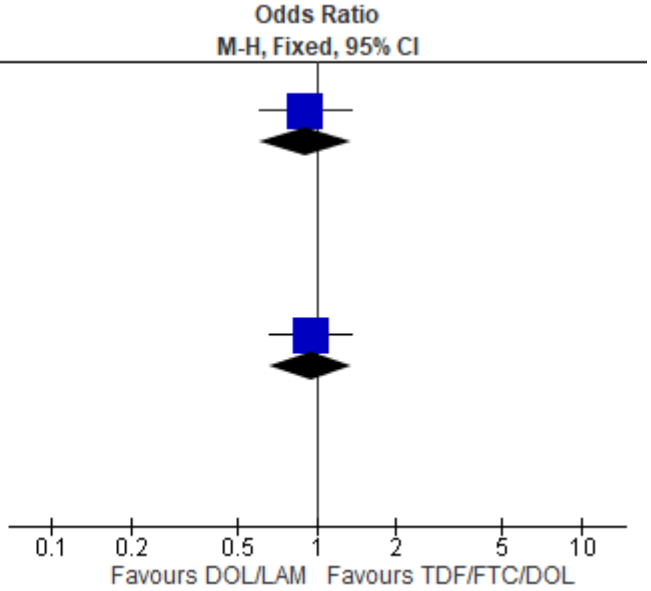
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.81), I² = 0%

Serious adverse events

Forest plot of comparison: 6 DOL/LAM vs TDF/FTC/DOL, outcome: 6.5 Serious AE.

Study or Subgroup	DOL/LAM Events	DOL/LAM Total	TDF/FTC/DOL Events	TDF/FTC/DOL Total	Weight	Odds Ratio M-H, Fixed, 95% CI
6.5.1 48 weeks						
GEMINI-1/2; Cahn 2019	50	716	55	717	100.0%	0.90 [0.61, 1.35]
Subtotal (95% CI)		**716**		**717**	**100.0%**	**0.90 [0.61, 1.35]**
Total events	50		55			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.50 (P = 0.62)						
6.5.2 96 weeks						
GEMINI-1/2; Cahn 2020	64	716	67	717	100.0%	0.95 [0.66, 1.36]
Subtotal (95% CI)		**716**		**717**	**100.0%**	**0.95 [0.66, 1.36]**
Total events	64		67			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						

Test for subgroup differences: $Chi^2 = 0.04$, df = 1 (P = 0.85), $I^2 = 0\%$

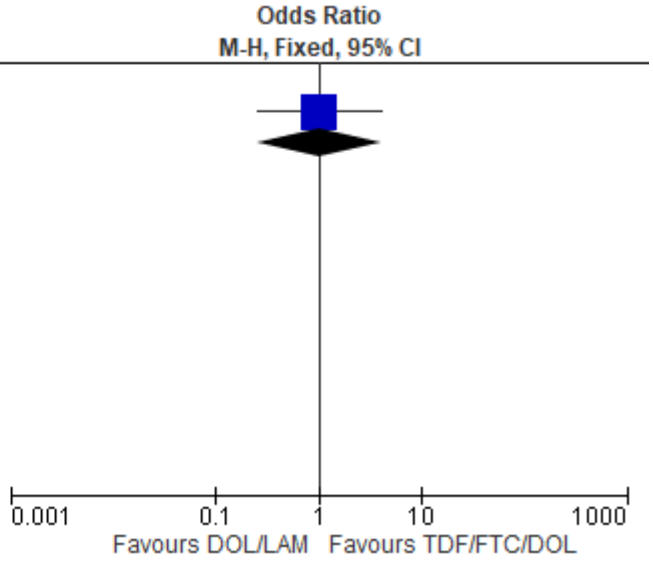


Drug-related SAE

Forest plot of comparison: 6 DOL/LAM vs TDF/FTC/DOL, outcome: 6.6 Drug-related serious AE.

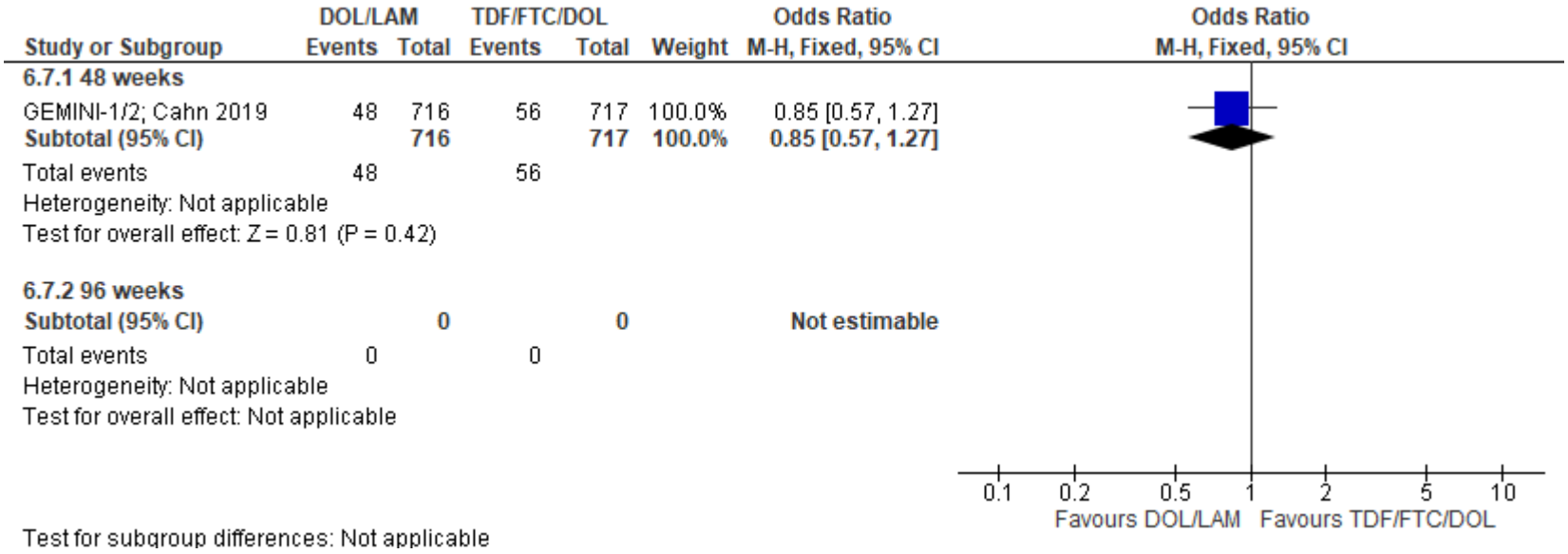
Study or Subgroup	DOL/LAM Events	DOL/LAM Total	TDF/FTC/DOL Events	TDF/FTC/DOL Total	Weight	Odds Ratio M-H, Fixed, 95% CI
6.6.1 48 weeks						
GEMINI-1/2; Cahn 2019	4	716	4	717	100.0%	1.00 [0.25, 4.02]
Subtotal (95% CI)		**716**		**717**	**100.0%**	**1.00 [0.25, 4.02]**
Total events	4		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
6.6.2 96 weeks						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

Test for subgroup differences: Not applicable



Grade 3/4 AE

Forest plot of comparison: 6 DOL/LAM vs TDF/FTC/DOL, outcome: 6.7 Grade 3/4 AE.

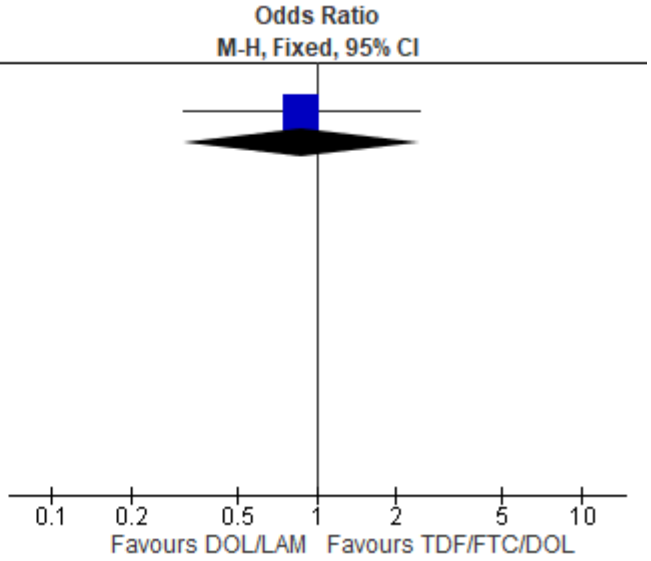


Drug-related Grade 3/4 AE

Forest plot of comparison: 6 DOL/LAM vs TDF/FTC/DOL, outcome: 6.8 Drug-related grade 3/4 AE.

Study or Subgroup	DOL/LAM Events	DOL/LAM Total	TDF/FTC/DOL Events	TDF/FTC/DOL Total	Weight	Odds Ratio M-H, Fixed, 95% CI
6.8.1 48 weeks						
GEMINI-1/2; Cahn 2019	7	716	8	717	100.0%	0.88 [0.32, 2.43]
Subtotal (95% CI)		**716**		**717**	**100.0%**	**0.88 [0.32, 2.43]**
Total events	7		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						
6.8.2 96 weeks						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

Test for subgroup differences: Not applicable



GRADE table for critical outcomes

Outcomes	Anticipated absolute effects* (95% CI) Risk with TDF/FTC/DOL	Anticipated absolute effects* (95% CI) Risk with DOL/LAM	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Virological success - 48 weeks	933 per 1,000	**915 per 1,000** (879 to 941)	**OR 0.77** (0.52 to 1.14)	1433 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Virological success - 96 weeks	895 per 1,000	**860 per 1,000** (817 to 894)	**OR 0.72** (0.52 to 0.99)	1433 (1 RCT)	⨁⨁⨁◯ Moderate[a]	
Virological failure - 48 weeks	18 per 1,000	**28 per 1,000** (14 to 55)	**OR 1.56** (0.77 to 3.15)	1433 (1 RCT)	⨁⨁◯◯ Low[a,b]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TDF/FTC/DOL	Risk with DOL/LAM				
Virological failure - 96 weeks	20 per 1,000	**31 per 1,000** (16 to 59)	**OR 1.59** (0.81 to 3.14)	1433 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Failure with resistance - 48 weeks	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	10 (1 RCT)	-	No events in either group
Failure with resistance - 96 weeks	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	18 (1 RCT)	-	No events in either group
AE-driven discontinuation - 48 weeks	22 per 1,000	**21 per 1,000** (10 to 42)	**OR 0.94** (0.46 to 1.91)	1433 (1 RCT)	⨁⨁◯◯ Low[a,b]	
AE-driven discontinuation - 96 weeks	32 per 1,000	**34 per 1,000** (19 to 58)	**OR 1.05** (0.59 to 1.87)	1433 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Serious AE - 48 weeks	77 per 1,000	**70 per 1,000** (48 to 101)	**OR 0.90** (0.61 to 1.35)	1433 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Serious AE - 96 weeks	93 per 1,000	**89 per 1,000** (64 to 123)	**OR 0.95** (0.66 to 1.36)	1433 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Drug-related serious AE - 48 weeks	6 per 1,000	**6 per 1,000** (1 to 22)	**OR 1.00** (0.25 to 4.02)	1433 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Drug-related serious AE - 96 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome
Grade 3/4 AE - 48 weeks	78 per 1,000	**67 per 1,000** (46 to 97)	**OR 0.85** (0.57 to 1.27)	1433 (1 RCT)	⨁⨁◯◯ Low[a,b]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TDF/FTC/DOL	**Risk with DOL/LAM**				
Grade 3/4 AE - 96 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome
Drug-related grade 3/4 AE - 48 weeks	11 per 1,000	**10 per 1,000** (4 to 27)	**OR 0.88** (0.32 to 2.43)	1433 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Drug-related grade 3/4 AE - 96 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. The study population was predominantly white (69%), male (85%) and aged <50 years at enrolment (90%); few participants were enrolled with baseline CD4+ cell count ≤200 cells/mm3, or with very high viral loads; those with hepatitis B virus infection or any major drug-resistance mutations were excluded.

b. 95% Confidence interval spans 1

7 DOL vs RALT + any 2 NRTIs

One study was included: SPRING-2; data were reported for 48 weeks (Raffi 2013a) and 96 weeks (Raffi 2013b).

Table 13. Key features of the included studies

Study name/ NCT number	Citation	Inclusion criteria	Exclusions	Population (n; demographics)	Intervention	Comparator	Outcomes
NCT01227824; SPRING-2	Raffi F, Rachlis A, Stellbrink HJ, Hardy WD, Torti C, Orkin C, Bloch M, Podzamczer D, Pokrovsky V, Pulido F, Almond S, Margolis D, Brennan C, Min S; SPRING-2 Study Group. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet. 2013 Mar 2;381(9868):735-43. doi: 10.1016/S0140-6736(12)61853-4. Epub 2013 Jan 8. PMID: 23306000.	≥18 years; naive for antiretroviral therapy with HIV-1 infection and HIV-1 RNA ≥1000 copies per mL; no primary resistance in reverse transcriptase or protease enzymes	Patients with active US Centers for Disease Control and Prevention category C disease, except for Kaposi's sarcoma. We also excluded patients with defi ned laboratory values or medical characteristics, including pregnancy; moderate or severe hepatic impairment; an anticipated need for hepatitis C treatment during the study; estimated creatinine clearance of less than 50 mL/min; recent or ongoing malignancy; or treatment with an HIV-1 vaccine within 90 days of screening or with any immunomodulator within 28 days. Patients could receive abacavir only after exclusion of the HLA-B*5701 allele	822 participants. Dolutegravir (n=411); Raltegravir (n=411) Median age (range; years) 37 (18–68); 35 (18–75) Men 348 (85%); 355 (86%) Race White 346 (84%); 352 (86%) Black 49 (12%); 39 (9%) Other 16 (4%); 20 (5%) Baseline HIV-1 RNA Median concentration (log10 copies per mL) 4.52 (4.08–5.06); 4.58 (4.12–5.07) >100 000 copies per mL 114 (28%) ;116 (28%) Baseline CD4 cell count	Dolutegravir. At the investigators' discretion, patients received an NRTI backbone of coformulated tenofovir/ emtricitabine or abacavir/lamivudine	Raltegravir. At the investigators' discretion, patients received an NRTI backbone of coformulated tenofovir/ emtricitabine or abacavir/lamivudine	The prespecified primary endpoint was the proportion of patients with HIV-1 RNA of less than 50 copies per mL at week 48. Main secondary endpoints were changes from baseline in CD4 cell counts, incidence and severity of adverse events, changes in laboratory parameters, and genotypic or phenotypic evidence of resistance. Other secondary endpoints were dolutegravir pharmacokinetics, pharmacokinetic and pharma codynamic relations, and health outcomes. The authors used EQ-5D (EuroQol, Rotterdam, Netherlands), a generic, non-disease-specific, preference-based utility measure that includes a

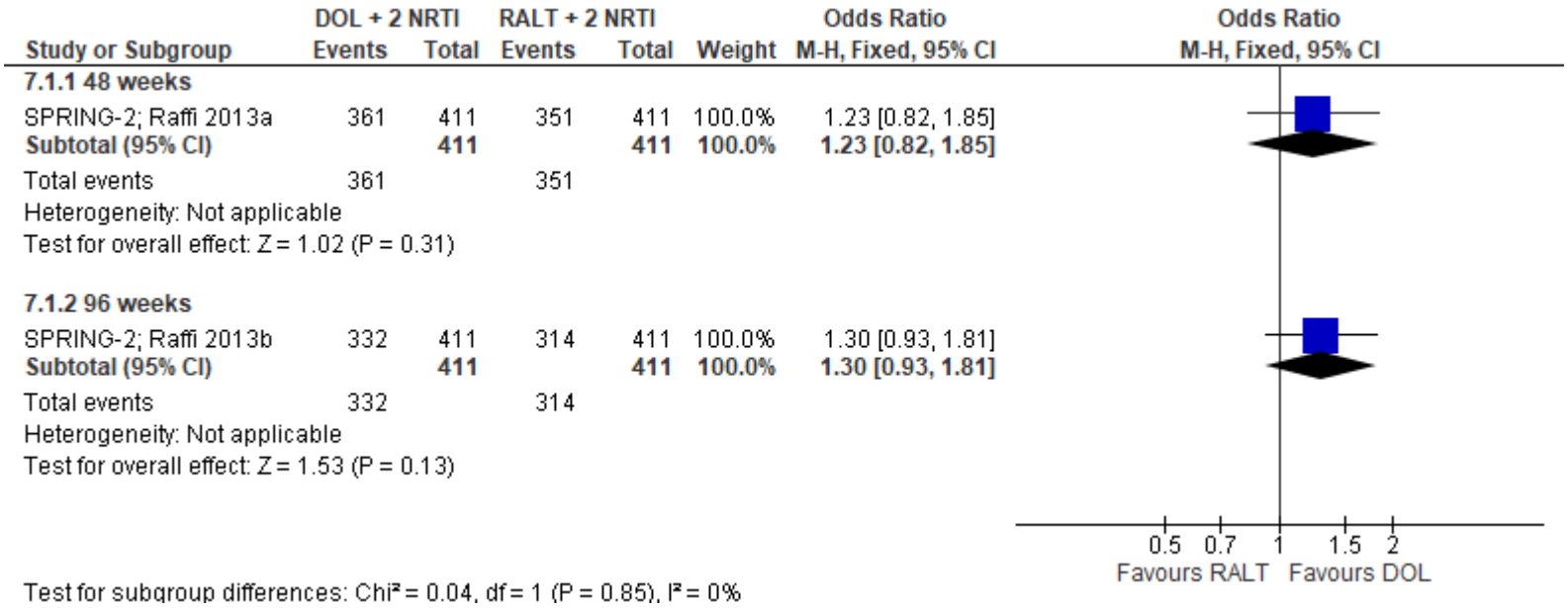
				Median (cells per µL) 359 (276–470); 362 (267–469)			descriptive system and a visual analogue scale, to measure health outcome
	Raffi F, Jaeger H, Quiros-Roldan E, Albrecht H, Belonosova E, Gatell JM, Baril JG, Domingo P, Brennan C, Almond S, Min S; extended SPRING-2 Study Group. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis. 2013 Nov;13(11):927-35. doi: 10.1016/S1473-3099(13)70257-3. Epub 2013 Sep 25. PMID: 24074642.	As above	As above	As above	As above	As above	As above

Table 14. Comparisons included in this section

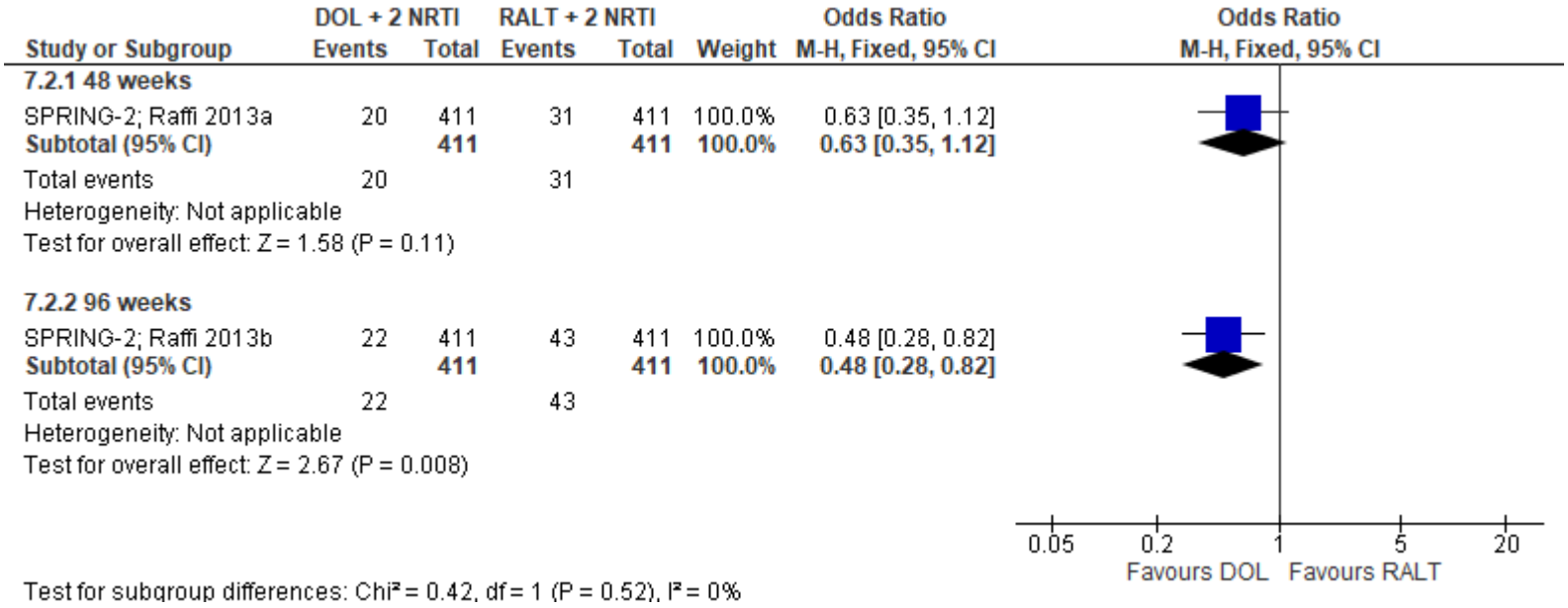
Study name/ NCT number	Intervention (DOL + 2 NRTIs)	Comparator (RALT + 2 NRTIs)
NCT01227824; SPRING-2	Dolutegravir. At the investigators' discretion, patients received an NRTI backbone of coformulated tenofovir [DF]/ emtricitabine or abacavir/lamivudine	Raltegravir. At the investigators' discretion, patients received an NRTI backbone of coformulated tenofovir [DF]/ emtricitabine or abacavir/lamivudine

Virological success, failure and missing data

Forest plot of comparison: 7 DOL vs RALT + any 2 NRTI, outcome: 7.1 Virological success.



Forest plot of comparison: 7 DOL vs RALT + any 2 NRTI, outcome: 7.2 Virological failure.



The difference between week 48 and week 96 responses was driven mainly by discontinuations for reasons other than adverse events; the proportion of virological non-response was unchanged for dolutegravir from week 48 to week 96, whereas it rose by 2% for raltegravir from week 48 to week 96.

Figure 13. Success, failure and missing data at 48 weeks

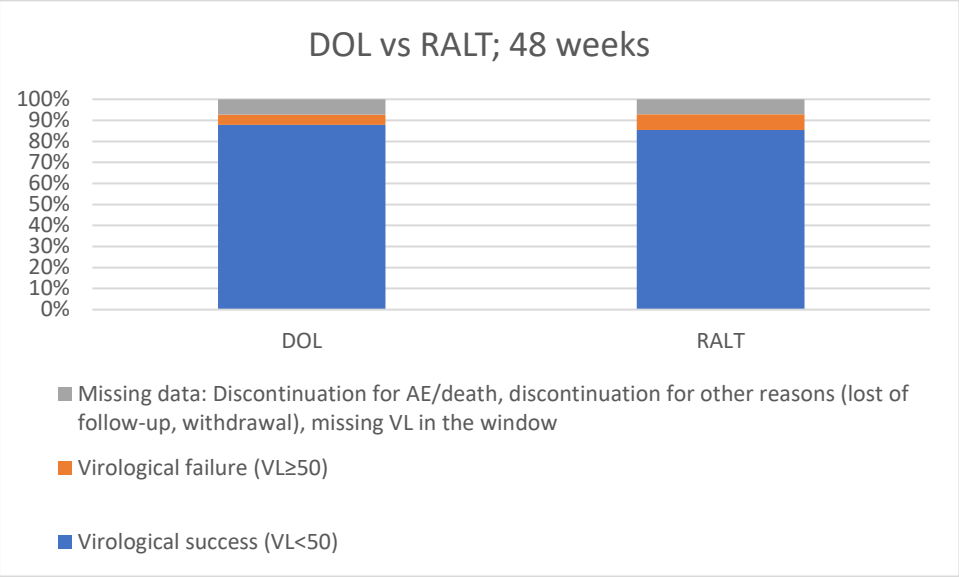
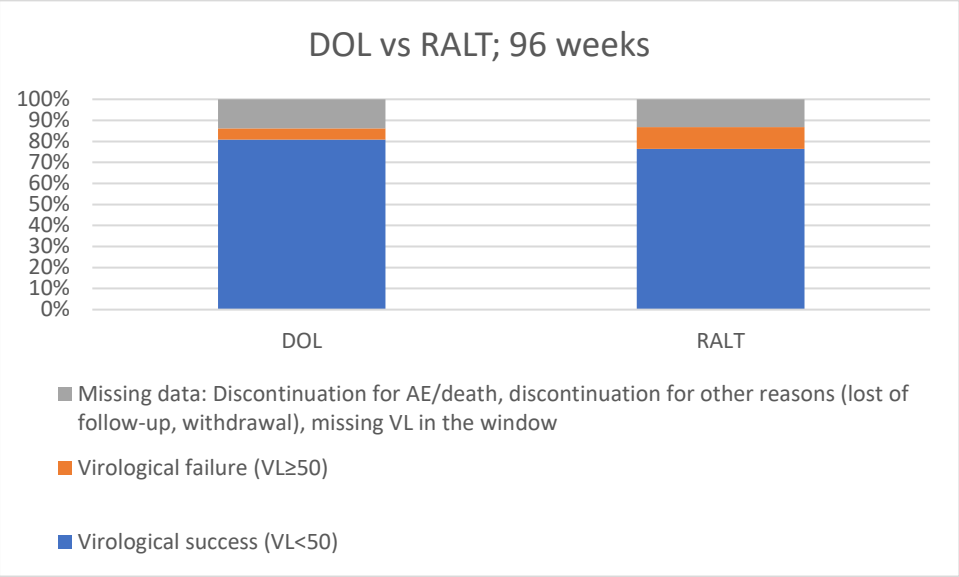


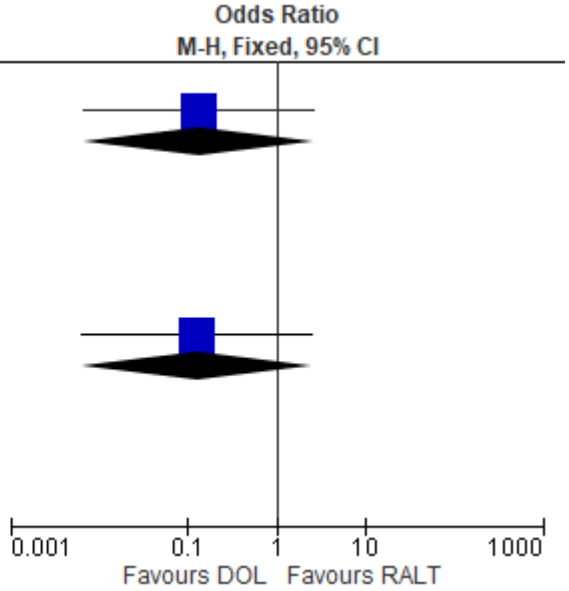
Figure 14. Success, failure and missing data at 96 weeks



Failing with resistance

Forest plot of comparison: 7 DOL vs RALT + any 2 NRTI, outcome: 7.3 Failure with resistance.

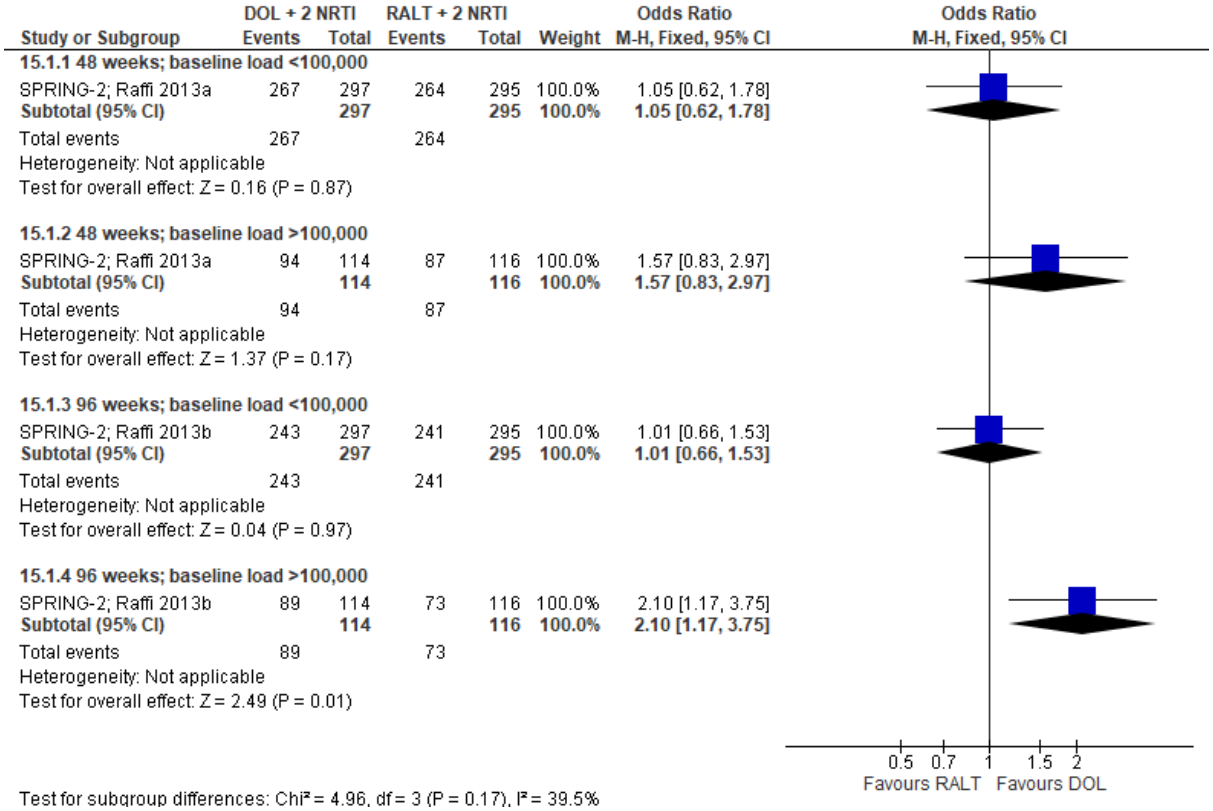
Study or Subgroup	DOL + 2 NRTI Events	Total	RALT + 2 NRTI Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
7.3.1 48 weeks						
SPRING-2; Raffi 2013a	0	20	4	28	100.0%	0.13 [0.01, 2.61]
Subtotal (95% CI)		**20**		**28**	**100.0%**	**0.13 [0.01, 2.61]**
Total events	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.33 (P = 0.18)						
7.3.2 96 weeks						
SPRING-2; Raffi 2013b	0	22	4	29	100.0%	0.13 [0.01, 2.47]
Subtotal (95% CI)		**22**		**29**	**100.0%**	**0.13 [0.01, 2.47]**
Total events	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.36 (P = 0.17)						



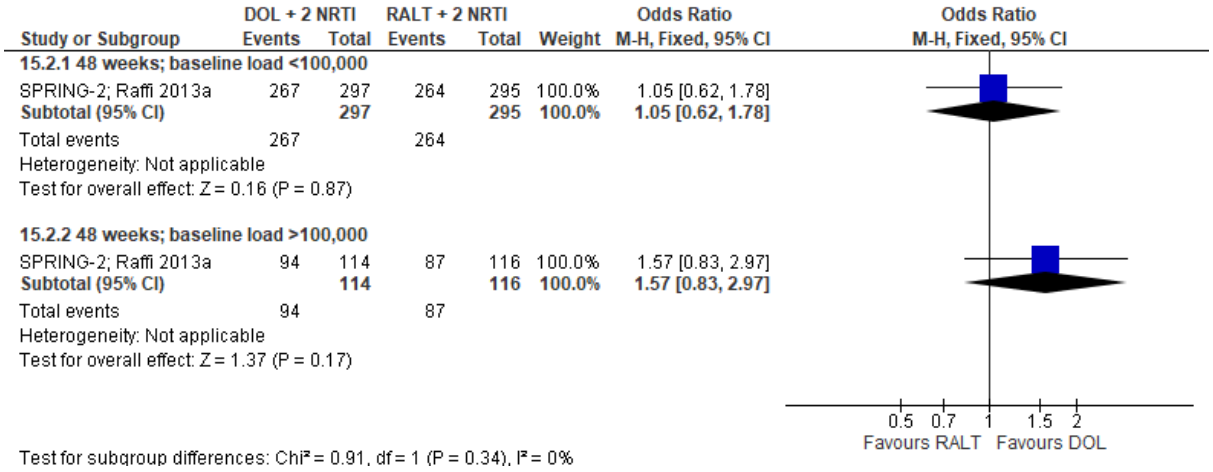
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.98), $I^2 = 0\%$

Raltegravir vs dolutegravir comparison by viral load (SPRING-2 study)

Forest plot of comparison: 15 DOL vs RALT + any 2 NRTI; subgroups by baseline viral load, outcome: 15.1 Virological success.

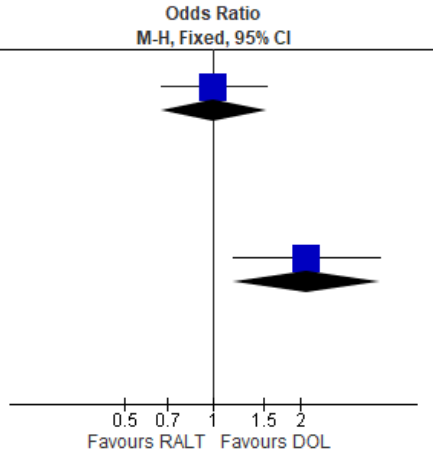


Forest plot of comparison: 15 DOL vs RALT + any 2 NRTI; subgroups by baseline viral load, outcome: 15.2 Virological success; week 48 only.



Forest plot of comparison: 15 DOL vs RALT + any 2 NRTI; subgroups by baseline viral load, outcome: 15.3 Virological success; week 96 only.

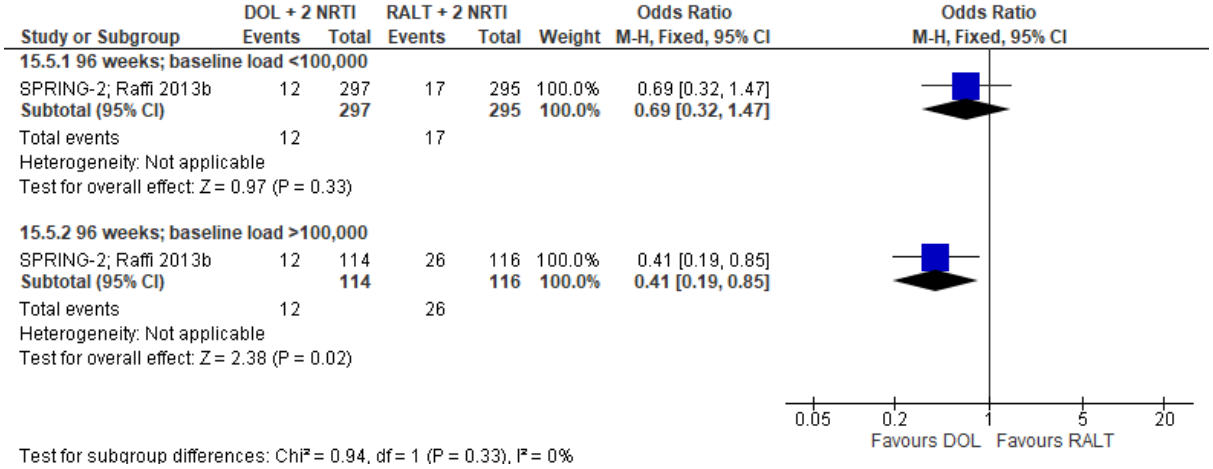
Study or Subgroup	DOL + 2 NRTI Events	Total	RALT + 2 NRTI Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
15.3.1 96 weeks; baseline load <100,000						
SPRING-2; Raffi 2013b	243	297	241	295	100.0%	1.01 [0.66, 1.53]
Subtotal (95% CI)		**297**		**295**	**100.0%**	**1.01 [0.66, 1.53]**
Total events	243		241			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.04 (P = 0.97)						
15.3.2 96 weeks; baseline load >100,000						
SPRING-2; Raffi 2013b	89	114	73	116	100.0%	2.10 [1.17, 3.75]
Subtotal (95% CI)		**114**		**116**	**100.0%**	**2.10 [1.17, 3.75]**
Total events	89		73			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.49 (P = 0.01)						



Test for subgroup differences: Chi² = 4.02, df = 1 (P = 0.05), I² = 75.1%

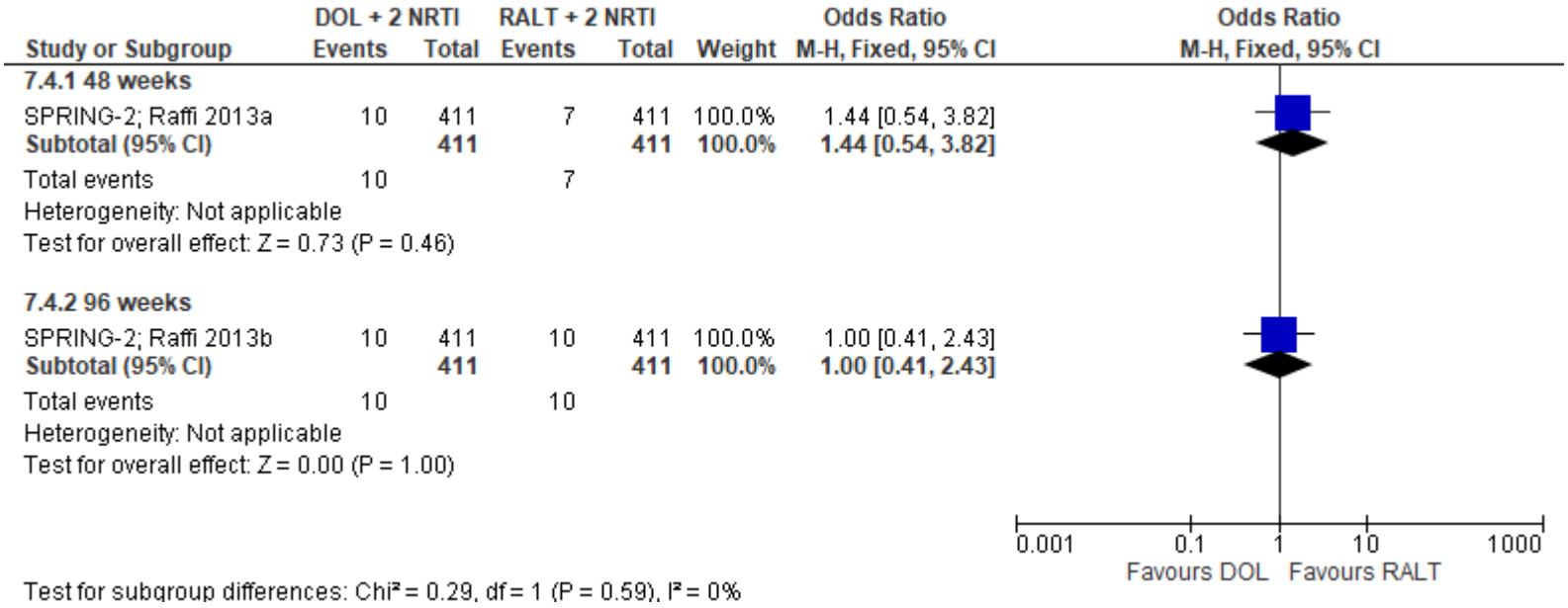
Virological failure: Raltegravir vs dolutegravir comparison by viral load (SPRING-2 study)

Forest plot of comparison: 15 DOL vs RALT + any 2 NRTI; subgroups by baseline viral load, outcome: 15.5 Virological failure; week 96 only.



Adverse event (AE)-driven discontinuation

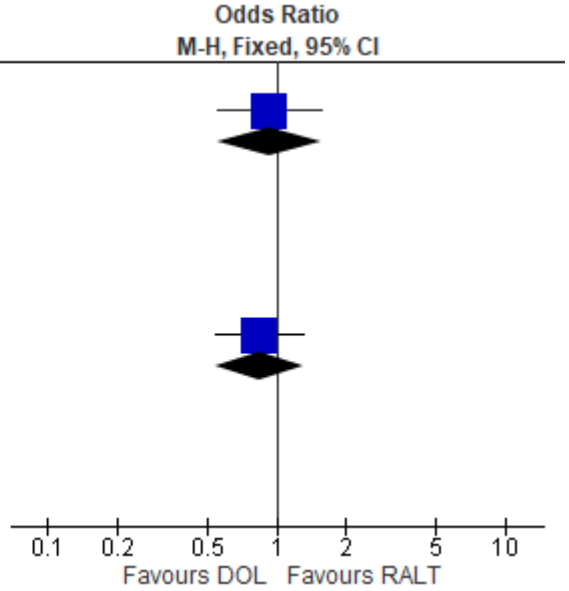
Forest plot of comparison: 7 DOL vs RALT + any 2 NRTI, outcome: 7.4 AE-driven discontinuation.



Serious adverse events

Forest plot of comparison: 7 DOL vs RALT + any 2 NRTI, outcome: 7.5 Serious AE.

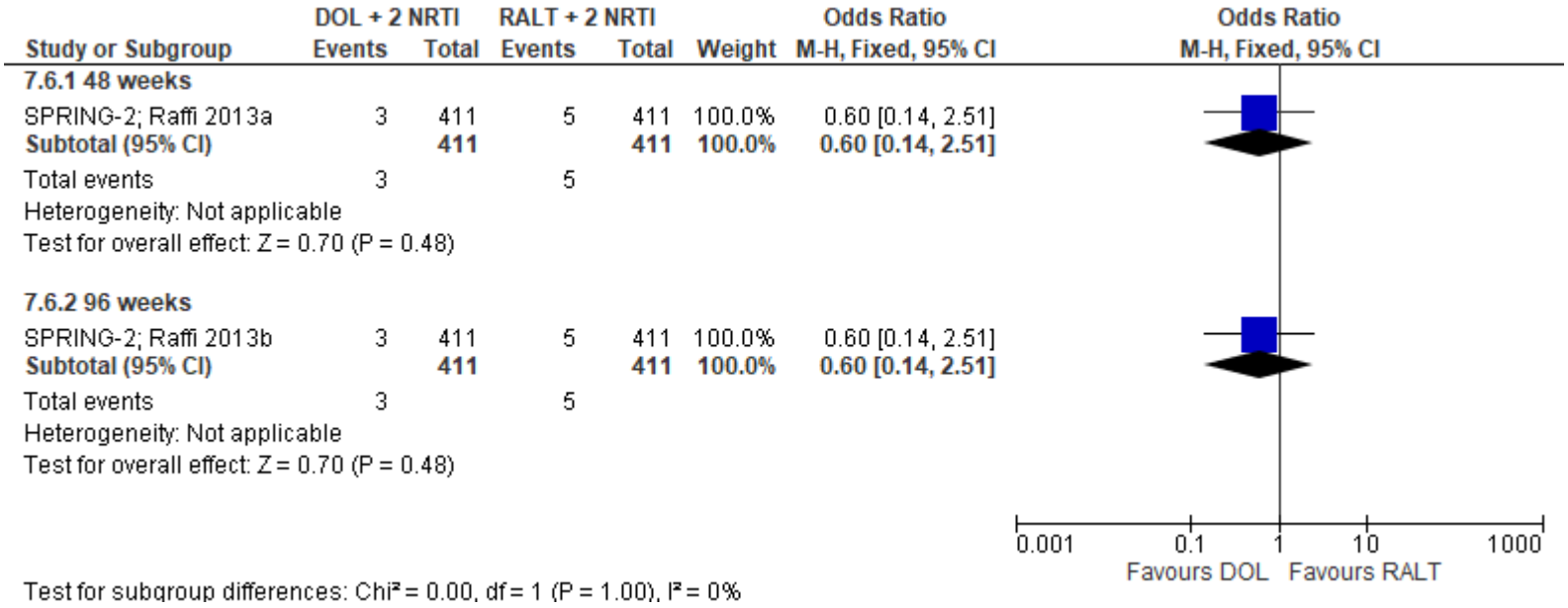
Study or Subgroup	DOL + 2 NRTI Events	Total	RALT + 2 NRTI Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
7.5.1 48 weeks						
SPRING-2; Raffi 2013a	29	411	31	411	100.0%	0.93 [0.55, 1.57]
Subtotal (95% CI)		**411**		**411**	**100.0%**	**0.93 [0.55, 1.57]**
Total events	29		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
7.5.2 96 weeks						
SPRING-2; Raffi 2013b	41	411	48	411	100.0%	0.84 [0.54, 1.30]
Subtotal (95% CI)		**411**		**411**	**100.0%**	**0.84 [0.54, 1.30]**
Total events	41		48			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						



Test for subgroup differences: $Chi^2 = 0.09$, df = 1 (P = 0.76), $I^2 = 0\%$

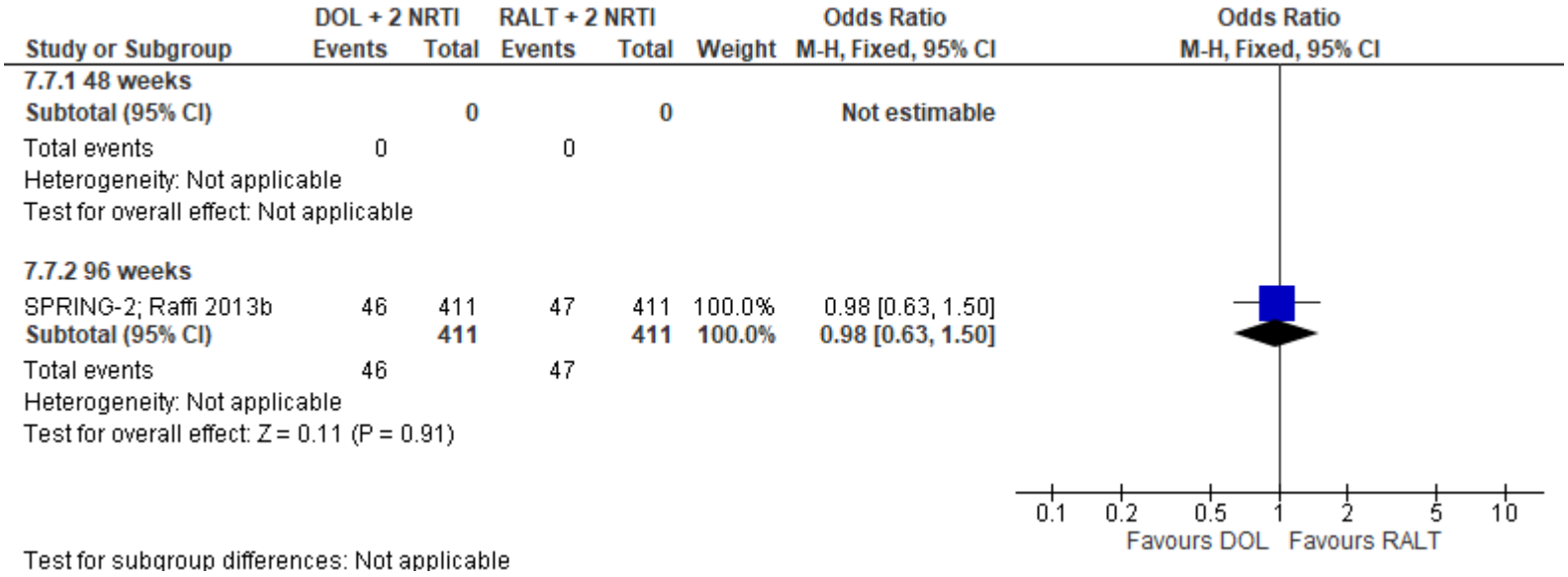
Drug-related SAE

Forest plot of comparison: 7 DOL vs RALT + any 2 NRTI, outcome: 7.6 Drug-related serious AE.



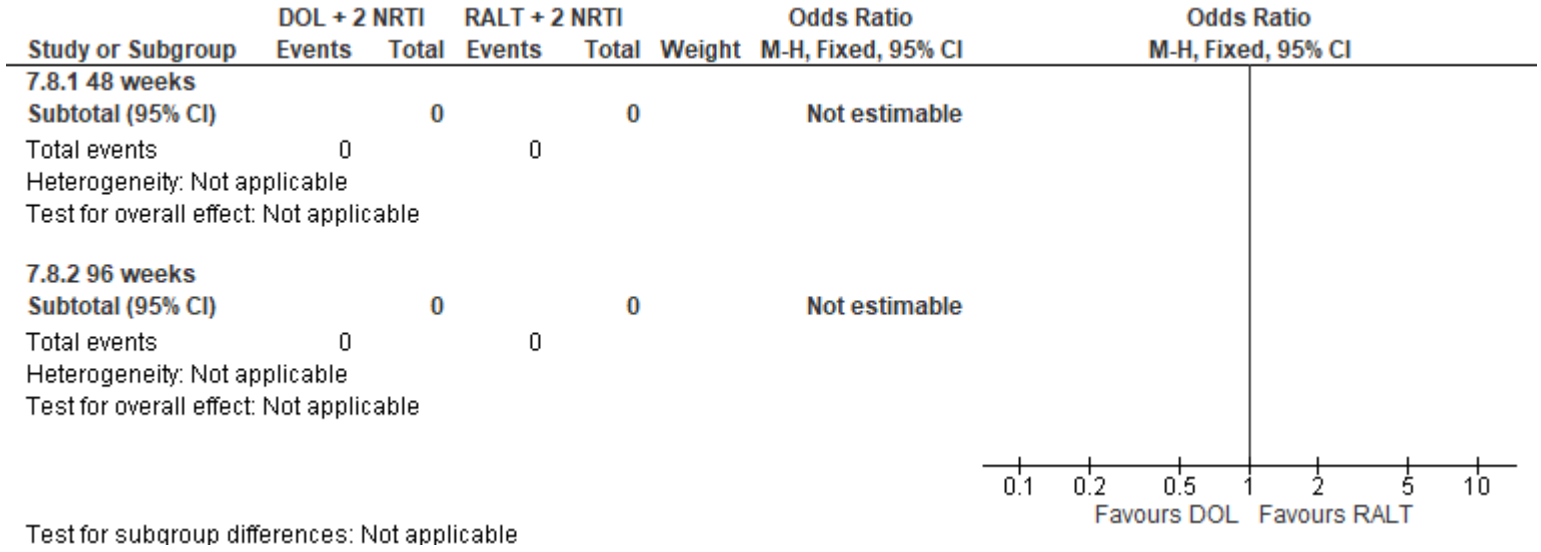
Grade 3/4 AE

Forest plot of comparison: 7 DOL vs RALT + any 2 NRTI, outcome: 7.7 Grade 3/4 AE.



Drug-related Grade 3/4 AE

Forest plot of comparison: 7 DOL vs RALT + any 2 NRTI, outcome: 7.8 Drug-related grade 3/4 AE.



GRADE table for critical outcomes

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with RALT + any 2 NRTI	**Risk with DOL**				
Virological success - 48 weeks	854 per 1,000	**878 per 1,000** (827 to 915)	**OR 1.23** (0.82 to 1.85)	822 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Virological success - 96 weeks	764 per 1,000	**808 per 1,000** (751 to 854)	**OR 1.30** (0.93 to 1.81)	822 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	
Virological failure - 48 weeks	75 per 1,000	**49 per 1,000** (28 to 84)	**OR 0.63** (0.35 to 1.12)	822 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Virological failure - 96 weeks	105 per 1,000	**53 per 1,000** (32 to 87)	**OR 0.48** (0.28 to 0.82)	822 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with RALT + any 2 NRTI	Risk with DOL				
Failure with resistance - 48 weeks	143 per 1,000	**21 per 1,000** (2 to 303)	**OR 0.13** (0.01 to 2.61)	48 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Failure with resistance - 96 weeks	138 per 1,000	**20 per 1,000** (2 to 283)	**OR 0.13** (0.01 to 2.47)	51 (1 RCT)	⨁⨁◯◯ Low[a,b]	
AE-driven discontinuation - 48 weeks	17 per 1,000	**24 per 1,000** (9 to 62)	**OR 1.44** (0.54 to 3.82)	822 (1 RCT)	⨁⨁◯◯ Low[a,b]	
AE-driven discontinuation - 96 weeks	24 per 1,000	**24 per 1,000** (10 to 57)	**OR 1.00** (0.41 to 2.43)	822 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Serious AE - 48 weeks	75 per 1,000	**71 per 1,000** (43 to 114)	**OR 0.93** (0.55 to 1.57)	822 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Serious AE - 96 weeks	117 per 1,000	**100 per 1,000** (67 to 147)	**OR 0.84** (0.54 to 1.30)	822 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Drug-related serious AE - 48 weeks	12 per 1,000	**7 per 1,000** (2 to 30)	**OR 0.60** (0.14 to 2.51)	822 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Drug-related serious AE - 96 weeks	12 per 1,000	**7 per 1,000** (2 to 30)	**OR 0.60** (0.14 to 2.51)	822 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Grade 3/4 AE - 48 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome
Grade 3/4 AE - 96 weeks	114 per 1,000	**112 per 1,000** (75 to 162)	**OR 0.98** (0.63 to 1.50)	822 (1 RCT)	⨁⨁◯◯ Low[a,b]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with RALT + any 2 NRTI	**Risk with DOL**				
Drug-related grade 3/4 AE - 48 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome
Drug-related grade 3/4 AE - 96 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. A limitation of this study is the low number of non-white and female patients enrolled, which is not fully representative of the HIV global epidemic

b. 95% Confidence interval includes 1

c. The difference between week 48 and week 96 responses was driven mainly by discontinuations for reasons other than adverse events; the proportion of virological non-response was unchanged for dolutegravir from week 48 to week 96, whereas it rose by 2% for raltegravir from week 48 to week 96

NRTI backbone comparison

8 TDF/FTC vs TAF/FTC with any 3rd agent

ADVANCE data were published for week 48 (Venter 2019) and week 96 results (Venter 2020). One paper (Sax 2015) reported on a pre-specified pooled analysis of two RCTs (week 48 outcomes): NCT01780506 (also known as GS-US-292-0104) and NCT01797445 (also known as GS-US-292-0111). These were identical protocols done at 134 sites in North America, Europe, Australia, Japan, and Thailand (GS-US-292-0104), and 128 sites in North America, Europe, and Latin America (GS-US-292-0111). Data from the AMBER study were published for week 48 (Eron 2018). Week 48 data were reported in the NCT01565850 (GS-US-299-0102) study (Mills 2015).

Table 15. Key features of the included studies

Study name/ NCT number	Citation	Inclusion criteria	Exclusions	Population (n; demographics)	Intervention	Comparator	Outcomes
NCT03122262; ADVANCE	Venter WDF, Moorhouse M, Sokhela S, Fairlie L, Mashabane N, Masenya M, Serenata C, Akpomiemie G, Qavi A, Chandiwana N, Norris S, Chersich M, Clayden P, Abrams E, Arulappan N, Vos A, McCann K, Simmons B, Hill A. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. N Engl J Med. 2019 Aug 29;381(9):803-815. doi: 10.1056/NEJMoa1902824. Epub 2019 Jul 24. PMID: 31339677.	Age ≥12 years, weight ≥40kg, viral load of ≥500 copies/mL, creatinine clearance >60 mL/min (Cockcroft–Gault formula) in patients 19 years of age or older or > 80 mL/min (modified Cockcroft–Gault formula) in those <19 years of age	>30 days of treatment with any form of ART, any ART within the past 6 months, pregnancy, or current treatment for tuberculosis	1053 participants with HIV infection in South Africa. The mean age was 32 years (range, 13 to 62); 14 patients were younger than 19 years of age. A total of 59% of the patients were female, more than 99% were black, and 62% were from South Africa. The mean CD4 count	Tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) and efavirenz (EFV) = TDF–FTC–EFV (standard-care group) OR Tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) and dolutegravir (DTG) = TDF–FTC–DTG (TDF-	Tenofovir alafenamide fumarate (TAF) plus emtricitabine (FTC) and dolutegravir (DTG) = TAF–FTC–DTG (TAF-based group)	The primary end point was the percentage of patients with an HIV-1 RNA level <50 copies/mL at week 48. Secondary objectives were to evaluate additional viral-load thresholds, CD4 count changes, and side-effect profile and safety, including

				was 337 cells per cubic millimeter (range, 1 to 1721), and 78% of the patients had a baseline HIV-1 RNA level of less than 100,000 copies per milliliter.	based group)		findings on physical examination, laboratory analyses, and dual-energy x-ray absorptiometry (DXA) scans.
	Venter, WDF; Sokhela, S; Simmons, B; Moorhouse, M; Fairlie, L; Mashabane, N; Serenata, C; Akpomiemie, G; Masenya, M; Qavi, A; Chandiwana, N; McCann, K; Norris, S; Chersich, M; Maartens, G; Lalla-Edward, S; Vos, A; Clayden, P; Abrams, E; Arulappan, N; Hill, A. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. The lancet. HIV 2020; 7(10): e666-676. DOI: 10.1016/S2352-3018(20)30241-1. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02192063/full	As above	As above	As above	As above	As above	As above
NCT01780506 (also known as GS-US-292-0104) and NCT01797445 (also known as GS-US-292-0111)	Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M, Pozniak A, Thompson M, Podzamczer D, Molina JM, Oka S, Koenig E, Trottier B, Andrade-Villanueva J, Crofoot G, Custodio JM, Plummer A, Zhong L, Cao H, Martin H, Callebaut C, Cheng AK, Fordyce MW, McCallister S; GS-US-292-0104/0111 Study Team. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet. 2015 Jun 27;385(9987):2606-15. doi: 10.1016/S0140-6736(15)60616-X. Epub 2015 Apr 15. Erratum in: Lancet. 2016 Apr 30;387(10030):1816. PMID: 25890673.	≥18 years; had HIV-1 and no previous antiretroviral treatment, had HIV-1 RNA concentration ≥1000 copies/mL, and an estimated glomerular filtration (creatinine	Patients with positive hepatitis B surface antigen or hepatitis C antibody or a new AIDS-defining illness within 30 days of screening	Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide (n=866); Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate (n=867) Age (years) 33 (26–42); 35 (28–44)	Elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate	Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide	The main outcomes were the proportion of patients with plasma HIV-1 RNA less than 50 copies per mL (non-inferiority margin of 12%) and pre-specified renal and bone

		clearance, Cockcroft-Gault) rate >50 mL/min; screening HIV-1 genotype showing sensitivity to elvitegravir, emtricitabine, and tenofovir		Women 133 (15%); 127 (15%) Ethnic origin White 485; (56%) 498 (57%) Black or African heritage 223 (26%); 213 (25%) Hispanic or Latino 167 (19%); 167 (19%) Asian 91 (11%); 89 (10%) HIV disease status: Asymptomatic 780 (90%); 802 (93%) Symptomatic: 53 (6%); 35 (4%) AIDS: 30 (4%); 26 (3%) HIV risk factor: Heterosexual sex 210 (24%); 219 (25%) Homosexual sex 652 (75%); 645 (74%) Intravenous drug use 5 (1%); 6 (1%)			endpoints at 48 weeks (centrally assessed). Secondary outcomes were percentage change from baseline in hip bone mineral density at week 48, percentage change from baseline in spine bone mineral density at week 48, change from baseline in serum creatinine at week 48, treatment-emergent proteinuria through week 48, proportion of participants with HIV-1 RNA lower than 20 per mL at week 48, change from baseline in CD4 cell count at week 48,

				Median HIV-1 RNA (log10 c/mL) 4.58 (4.04–4.95) 4.58 (4.15–4.96) HIV-1 RNA concentration >100 000 copies per mL 196 (23%); 195 (22%) Median CD4 count (cells per µL) 404 (283–550); 406 (291–542) Number with CD4 cell count (cells per µL) <50: 24 (3%); 27 (3%) ≥50 to <200: 88 (10%); 90 (10%) ≥200: 753 (87%); 750 (87%) Median estimated glomerular filtration rate (Cockcroft-Gault; mL/min) 117 (100–136); 114 (99–134) Median BMI			percentage change from baseline in urine retinol binding protein to creatinine ratio at week 48, percentage change from baseline in urine β2-microglobulin to creatinine ratio at week 48, percentage change from baseline in urine protein to creatinine ratio at week 48, and percentage change from baseline in urine albumin to creatinine ratio. Safety was assessed by physical examinations, laboratory tests, 12-lead electro-cardiogram, and recording of adverse events

				(kg/m²) 24.4 (22.0–28.0); 24.5 (21.7–28.0) Data are median (IQR) or n (%).			
NCT02431247; AMBER	Eron JJ, Orkin C, Gallant J, Molina JM, Negredo E, Antinori A, Mills A, Reynes J, Van Landuyt E, Lathouwers E, Hufkens V, Jezorwski J, Vanveggel S, Opsomer M; AMBER study group. A week-48 randomized phase-3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naive HIV-1 patients. AIDS. 2018 Jul 17;32(11):1431-1442. doi: 10.1097/QAD.0000000000001817. PMID: 29683855; PMCID: PMC6039393.	≥18 years; treatment-naive, HIV-1-infected with a screening plasma viral load >1000 copies/mL, CD4+ cell count >50 cells/mL, genotypic sensitivity to darunavir, emtricitabine, and tenofovir, and an estimated glomerular filtration rate based on serum creatinine (eGFRcr) ≥70 ml/min (Cockcroft–Gault formula)	Diagnosis of a new AIDS-defining condition within 30 days prior to screening, hepatitis B or C coinfection, clinically significant disease (e.g. malignancy, severe infections), and pregnancy or breast-feeding in women. Medications or herbal supplements known or suspected to have drug interactions with the investigational medications were disallowed.	725 participants. Median age was 34 years, 88% were men, 83% were white, and 18% had viral load at least 100 000 copies/mL. Median baseline CD4+ cell count was 453 cells/mL	Darunavir/ cobicistat plus emtricitabine/ tenofovir disoproxyl fumarate (TDF)	Darunavir/ cobicistat/ emtricitabine/ tenofovir alafenamide (D/C/F/TAF)	Primary: proportion of patients with viral load <50 copies/mL (response rate) by the Food and Drug Administration (FDA)-snapshot analysis. Secondary outcomes included proportion of patients with viral load <20 and <200 copies/mL (FDA-snapshot analysis) and viral load <50 copies/mL (time-to-loss-of-virologic-response algorithm) at week 48; changes from baseline in log10 viral load and

							CD4+ cell count; antiretroviral resistance development in PDVFs; safety and tolerability through 48 weeks; changes from baseline in serum creatinine, eGFRcr, eGFRcyst, and ratios of total urine protein, urine albumin, urine RBP, and beta-2-microglobulin to creatinine.
NCT01565850 (GS-US-299-0102)	Mills A, Crofoot G Jr, McDonald C, Shalit P, Flamm JA, Gathe J Jr, Scribner A, Shamblaw D, Saag M, Cao H, Martin H, Das M, Thomas A, Liu HC, Yan M, Callebaut C, Custodio J, Cheng A, McCallister S. Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate in the First Protease Inhibitor-Based Single-Tablet Regimen for Initial HIV-1 Therapy: A Randomized Phase 2 Study. J Acquir Immune Defic Syndr. 2015 Aug 1;69(4):439-45. doi: 10.1097/QAI.0000000000000618. PMID: 25867913.	≥18 years; HIV-positive, treatment-naive with plasma HIV-1 RNA ≥5000 copies/mL and CD4+ cell count >50 cells per microliter. Genotype sensitivity to DRV, TDF, and FTC,	Pregnant, hepatitis B or C coinfected, or had a new AIDS-defining condition within 30 days of screening	153 participants. 92.8% male; median age 33 years; 34.6% Black/African American and 20.9% were of Hispanic ethnicity. The median VL at baseline was 4.66 log10 copies/mL, and median CD4 count	Darunavir, cobicistat, emtricitabine, tenofovir disoproxil fumarate (TDF)	Darunavir, cobicistat, emtricitabine, tenofovir alafenamide (TAF)	HIV-1 RNA <50 copies/mL at week 24 (primary end point) and week 48 (secondary end point). NB This phase 2 study was not sufficiently powered for non-inferiority, but rather to provide

		and estimated glomerular filtration rate (eGFR) by Cockcroft–Gault formula (eGFRCG) ≥70 mL/min were required		was 384 cells per microliter with 80% of participants having an HIV-1 RNA VL ≤100,000 copies/mL and 14% of participants having a CD4 <200 cells per microliter. The median eGFRCG values were similar in the 2 treatment groups: TAF 116.0 mL/min and TDF 109.6 mL/min.			clinical data that would guide planning phase 3 studies.

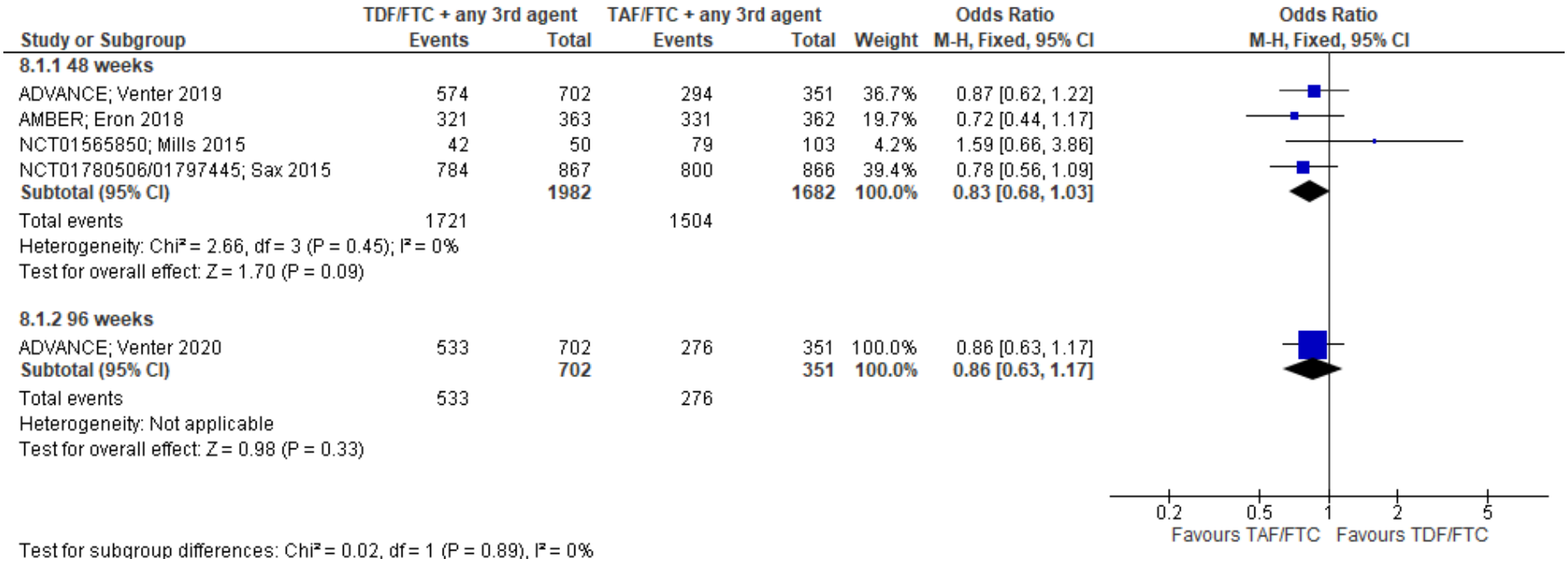
Table 16. Comparisons included in this section

Study name/ NCT number	Intervention (TDF/FTC with any 3rd agent)	Comparator (TAF/FTC with any 3rd agent)
NCT03122262; ADVANCE	Tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) and efavirenz (EFV) = TDF–FTC–EFV (standard-care group) OR Tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) and dolutegravir (DTG) = TDF–FTC–DTG (TDF-based group) The two groups were combined in the analyses.	Tenofovir alafenamide fumarate (TAF) plus emtricitabine (FTC) and dolutegravir (DTG) = TAF–FTC–DTG (TAF-based group)
NCT01780506 (also known as GS-US-292-0104) and NCT01797445 (also known as GS-US-292-0111)	Elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate	Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide
NCT02431247; AMBER	Darunavir, cobicistat, emtricitabine, tenofovir disoproxyl fumarate (TDF)	Darunavir, cobicistat, emtricitabine, tenofovir alafenamide (D/C/F/TAF)

NCT01565850 (GS-US-299-0102)	Darunavir, cobicistat, emtricitabine, tenofovir disoproxil fumarate (TDF)	Darunavir, cobicistat, emtricitabine, tenofovir alafenamide (TAF)

Virological success, failure and missing data

Forest plot of comparison: 8 TDF/FTC vs TAF/FTC + any 3rd agent, outcome: 8.1 Virological success.



Forest plot of comparison: 8 TDF/FTC vs TAF/FTC + any 3rd agent, outcome: 8.2 Virological failure.

Study or Subgroup	TDF/FTC + any 3rd agent Events	Total	TAF/FTC + any 3rd agent Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
8.2.1 48 weeks						
ADVANCE; Venter 2019	33	702	16	351	25.9%	1.03 [0.56, 1.90]
AMBER; Eron 2018	12	363	16	362	19.7%	0.74 [0.34, 1.59]
NCT01565850; Mills 2015	6	50	16	103	11.7%	0.74 [0.27, 2.03]
NCT01780506/01797445; Sax 2015	35	867	35	866	42.7%	1.00 [0.62, 1.61]
Subtotal (95% CI)		**1982**		**1682**	**100.0%**	**0.93 [0.67, 1.27]**
Total events	86		83			
Heterogeneity: Chi² = 0.74, df = 3 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.64)						
8.2.2 96 weeks						
ADVANCE; Venter 2020	29	702	11	351	100.0%	1.33 [0.66, 2.70]
Subtotal (95% CI)		**702**		**351**	**100.0%**	**1.33 [0.66, 2.70]**
Total events	29		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.80 (P = 0.43)						
Test for subgroup differences: Chi² = 0.84, df = 1 (P = 0.36), I² = 0%						

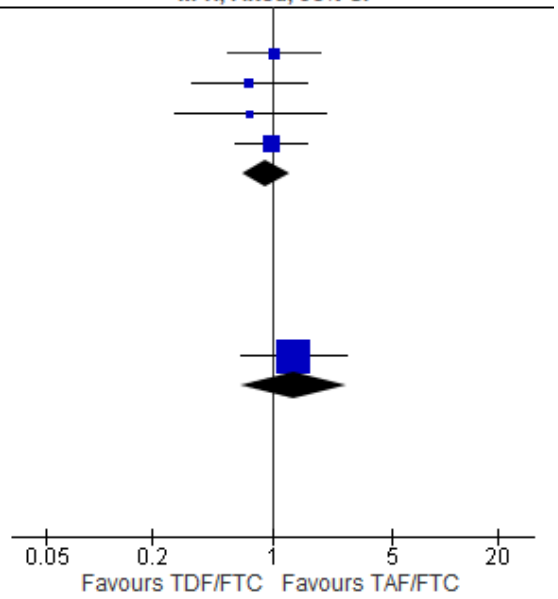
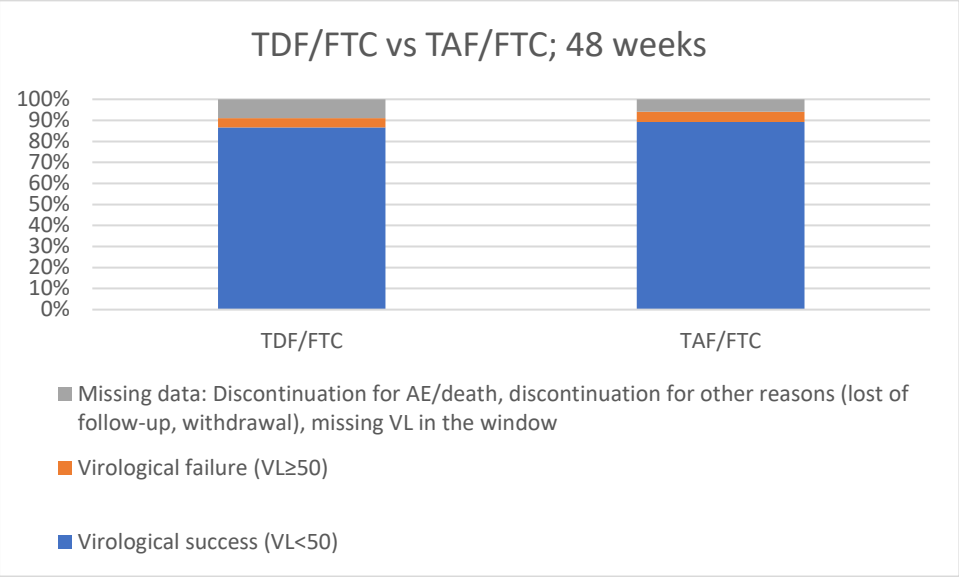
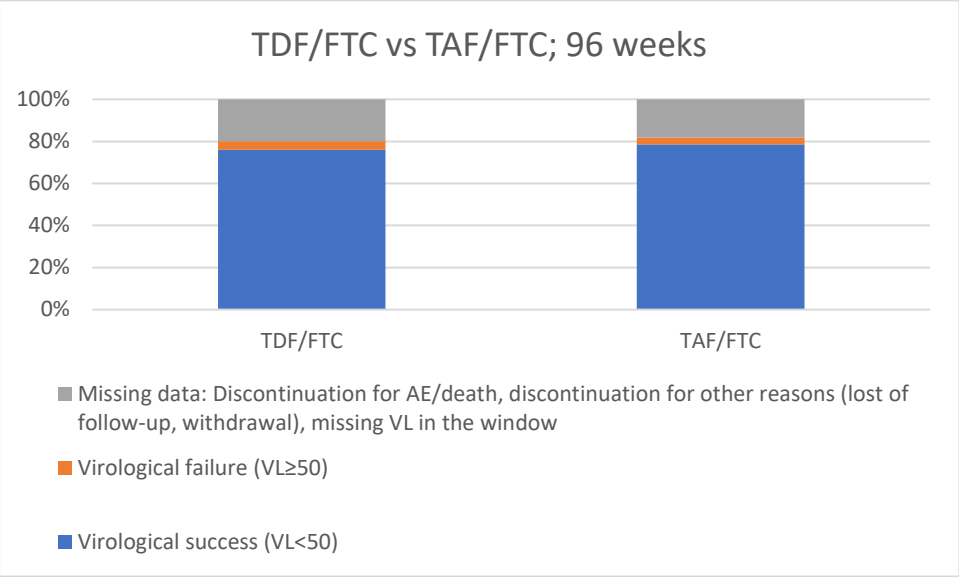


Figure 15. Success, failure and missing data at 48 weeks



Of note, the authors of the Mills 2015 study reported that the difference in virologic response rates at week 48 was primarily driven by the higher rate of participants in the TAF group (6.8%) compared with the TDF group (2%) who discontinued study drug with last available VL <50 copies/mL (e.g. due to reasons other than virologic failure such as loss to follow-up or investigator's discretion).

Figure 16. Success, failure and missing data at 96 weeks

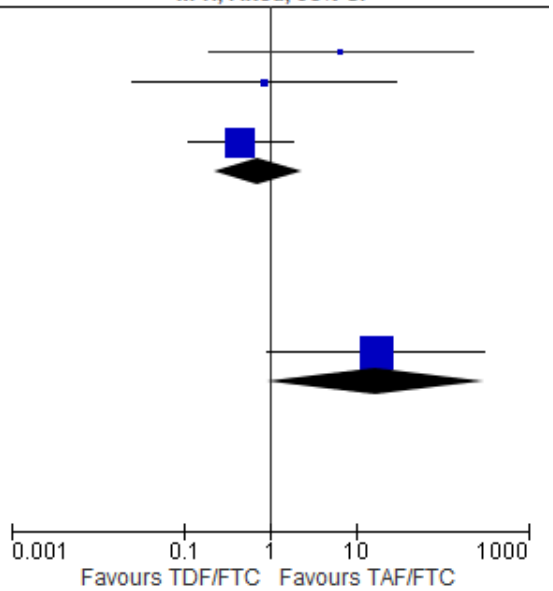


Failing with resistance

Forest plot of comparison: 8 TDF/FTC vs TAF/FTC + any 3rd agent, outcome: 8.3 Failure with resistance.

Study or Subgroup	TDF/FTC + any 3rd agent Events	Total	TAF/FTC + any 3rd agent Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
8.3.1 48 weeks						
ADVANCE; Venter 2019	5	7	0	1	3.8%	6.60 [0.19, 225.79]
AMBER; Eron 2018	0	2	1	7	10.4%	0.87 [0.03, 29.20]
NCT01565850; Mills 2015	0	6	0	16		Not estimable
NCT01780506/01797445; Sax 2015	5	19	7	16	85.7%	0.46 [0.11, 1.90]
Subtotal (95% CI)		**34**		**40**	**100.0%**	**0.74 [0.23, 2.38]**
Total events	10		8			
Heterogeneity: Chi² = 1.91, df = 2 (P = 0.38); I² = 0%						
Test for overall effect: Z = 0.51 (P = 0.61)						
8.3.2 96 weeks						
ADVANCE; Venter 2020	15	37	0	12	100.0%	17.22 [0.95, 312.93]
Subtotal (95% CI)		**37**		**12**	**100.0%**	**17.22 [0.95, 312.93]**
Total events	15		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.92 (P = 0.05)						

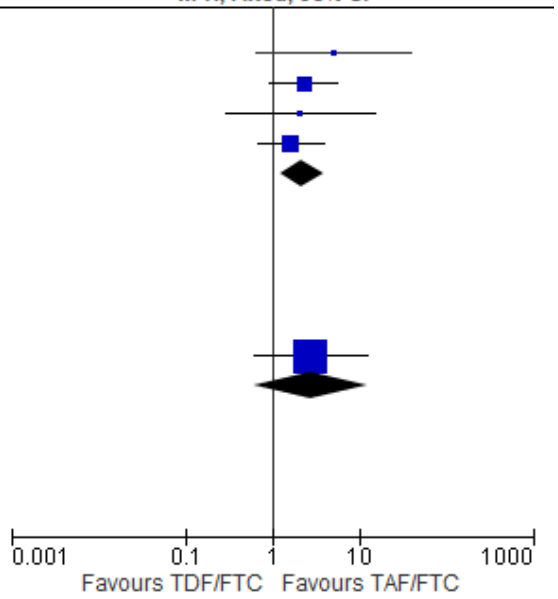
Test for subgroup differences: Chi² = 3.90, df = 1 (P = 0.05), I² = 74.3%



Adverse event (AE)-driven discontinuation

Forest plot of comparison: 8 TDF/FTC vs TAF/FTC + any 3rd agent, outcome: 8.4 AE-driven discontinuation.

Study or Subgroup	TDF/FTC + any 3rd agent Events	Total	TAF/FTC + any 3rd agent Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
8.4.1 48 weeks						
ADVANCE; Venter 2019	10	702	1	351	7.7%	5.06 [0.64, 39.67]
AMBER; Eron 2018	16	363	7	362	39.1%	2.34 [0.95, 5.75]
NCT01565850; Mills 2015	2	50	2	103	7.3%	2.10 [0.29, 15.39]
NCT01780506/01797445; Sax 2015	13	867	8	866	46.0%	1.63 [0.67, 3.96]
Subtotal (95% CI)		**1982**		**1682**	**100.0%**	**2.21 [1.25, 3.90]**
Total events	41		18			
Heterogeneity: Chi² = 1.08, df = 3 (P = 0.78); I² = 0%						
Test for overall effect: Z = 2.72 (P = 0.007)						
8.4.2 96 weeks						
ADVANCE; Venter 2020	11	702	2	351	100.0%	2.78 [0.61, 12.60]
Subtotal (95% CI)		**702**		**351**	**100.0%**	**2.78 [0.61, 12.60]**
Total events	11		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.32 (P = 0.19)						

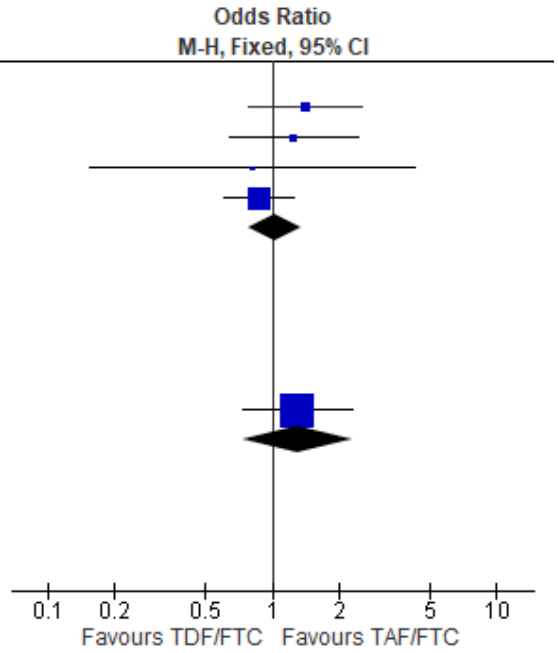


Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%

Serious adverse events

Forest plot of comparison: 8 TDF/FTC vs TAF/FTC + any 3rd agent, outcome: 8.5 Serious AE.

Study or Subgroup	TDF/FTC + any 3rd agent Events	Total	TAF/FTC + any 3rd agent Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
8.5.1 48 weeks						
ADVANCE; Venter 2019	44	702	16	351	19.3%	1.40 [0.78, 2.52]
AMBER; Eron 2018	21	363	17	362	15.5%	1.25 [0.65, 2.40]
NCT01565850; Mills 2015	2	50	5	103	3.0%	0.82 [0.15, 4.36]
NCT01780506/01797445; Sax 2015	61	867	69	866	62.1%	0.87 [0.61, 1.25]
Subtotal (95% CI)		**1982**		**1682**	**100.0%**	**1.03 [0.79, 1.35]**
Total events	128		107			
Heterogeneity: Chi² = 2.25, df = 3 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.23 (P = 0.82)						
8.5.2 96 weeks						
ADVANCE; Venter 2020	46	702	18	351	100.0%	1.30 [0.74, 2.27]
Subtotal (95% CI)		**702**		**351**	**100.0%**	**1.30 [0.74, 2.27]**
Total events	46		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.91 (P = 0.36)						
Test for subgroup differences: Chi² = 0.52, df = 1 (P = 0.47), I² = 0%						

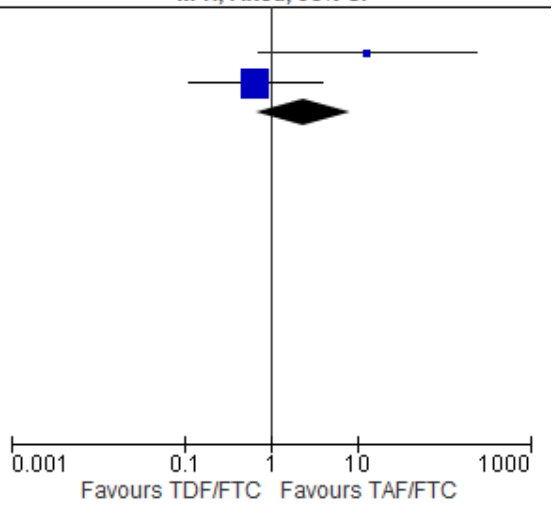


Drug-related SAE

Forest plot of comparison: 8 TDF/FTC vs TAF/FTC + any 3rd agent, outcome: 8.6 Drug-related serious AE.

Study or Subgroup	TDF/FTC + any 3rd agent Events	Total	TAF/FTC + any 3rd agent Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
8.6.1 48 weeks						
AMBER; Eron 2018	6	363	0	362	14.1%	13.18 [0.74, 234.86]
NCT01780506/01797445; Sax 2015	2	867	3	866	85.9%	0.67 [0.11, 3.99]
Subtotal (95% CI)		**1230**		**1228**	**100.0%**	**2.43 [0.70, 8.45]**
Total events	8		3			
Heterogeneity: Chi² = 3.33, df = 1 (P = 0.07); I² = 70%						
Test for overall effect: Z = 1.40 (P = 0.16)						
8.6.2 96 weeks						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

Test for subgroup differences: Not applicable

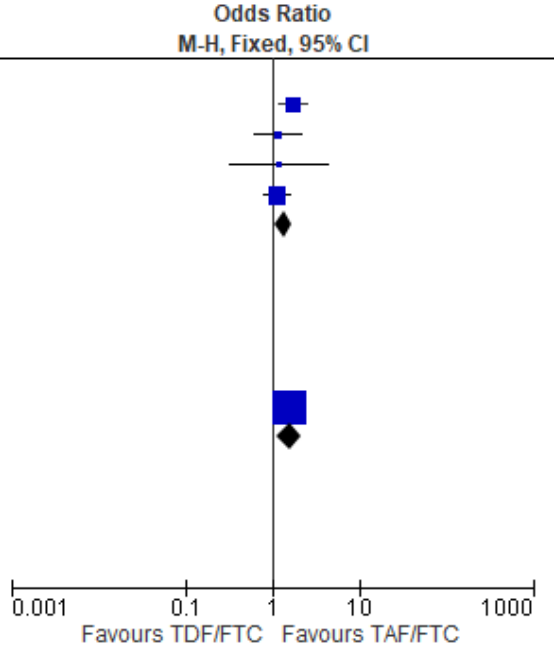


Grade 3/4 AE

Forest plot of comparison: 8 TDF/FTC vs TAF/FTC + any 3rd agent, outcome: 8.7 Grade 3/4 AE.

Study or Subgroup	TDF/FTC + any 3rd agent Events	Total	TAF/FTC + any 3rd agent Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
8.7.1 48 weeks						
ADVANCE; Venter 2019	136	702	42	351	34.7%	1.77 [1.22, 2.57]
AMBER; Eron 2018	22	363	19	362	13.7%	1.16 [0.62, 2.19]
NCT01565850; Mills 2015	4	50	7	103	3.2%	1.19 [0.33, 4.28]
NCT01780506/01797445; Sax 2015	78	867	69	866	48.3%	1.14 [0.81, 1.60]
Subtotal (95% CI)		**1982**		**1682**	**100.0%**	**1.36 [1.09, 1.71]**
Total events	240		137			
Heterogeneity: Chi² = 3.20, df = 3 (P = 0.36); I² = 6%						
Test for overall effect: Z = 2.68 (P = 0.007)						
8.7.2 96 weeks						
ADVANCE; Venter 2020	156	702	54	351	100.0%	1.57 [1.12, 2.21]
Subtotal (95% CI)		**702**		**351**	**100.0%**	**1.57 [1.12, 2.21]**
Total events	156		54			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.60 (P = 0.009)						

Test for subgroup differences: Chi² = 0.46, df = 1 (P = 0.50), I² = 0%



Of note, the originally published supplement for Sax 2015 reports data for Grade 3/4 AE as:

"Any Grade 3 or 4 AE: TAF: 8%; TDF: 0%"

However, the 0% in the TDF group must be an error as the drug-related Grade 3/4 AE is >0.

There is a further publication relating to this paper:

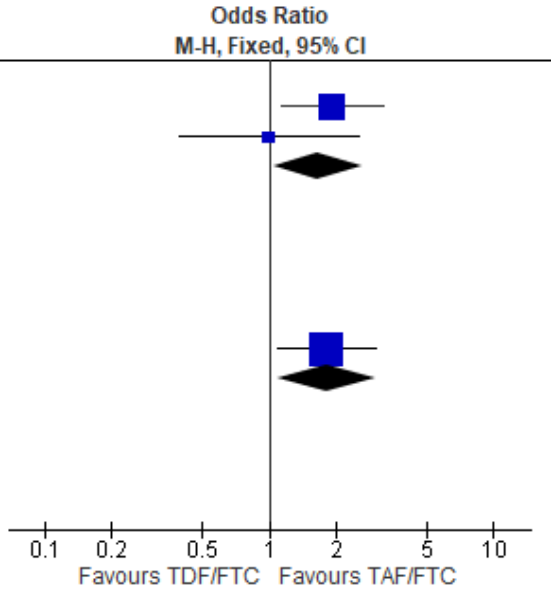
Department of Error (Department of Error (thelancet.com)): Sax PE, Wohl D, Yin MT, et al, for the GS-US-292-0104/0111 Study Team. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet 2015; 385: 2606–15—In this Article, in figure 2A, the 95% CI should have been –0·7 to 4·7. Additionally,

in table 3 in the appendix, the grade 3 or 4 AE row in the E/C/F/TDF group should have been 9%. This correction has been made to the online version and the appendix has been corrected as of April 28, 2016.

Drug-related Grade 3/4 AE

Forest plot of comparison: 8 TDF/FTC vs TAF/FTC + any 3rd agent, outcome: 8.8 Drug-related grade 3/4 AE.

Study or Subgroup	TDF/FTC + any 3rd agent Events	Total	TAF/FTC + any 3rd agent Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
8.8.1 48 weeks						
ADVANCE; Venter 2019	69	702	19	351	71.9%	1.90 [1.13, 3.22]
NCT01780506/01797445; Sax 2015	9	867	9	866	28.1%	1.00 [0.39, 2.53]
Subtotal (95% CI)		**1569**		**1217**	**100.0%**	**1.65 [1.05, 2.59]**
Total events	78		28			
Heterogeneity: Chi² = 1.41, df = 1 (P = 0.24); I² = 29%						
Test for overall effect: Z = 2.18 (P = 0.03)						
8.8.2 96 weeks						
ADVANCE; Venter 2020	72	702	21	351	100.0%	1.80 [1.08, 2.97]
Subtotal (95% CI)		**702**		**351**	**100.0%**	**1.80 [1.08, 2.97]**
Total events	72		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.28 (P = 0.02)						



Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%

GRADE table for critical outcomes

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TAF/FTC + any 3rd agent	Risk with TDF/FTC				
Virological success - 48 weeks	894 per 1,000	**875 per 1,000** (852 to 897)	**OR 0.83** (0.68 to 1.03)	3664 (4 RCTs)	⨁◯◯◯ Very low[a,b,c]	
Virological success - 96 weeks	786 per 1,000	**760 per 1,000** (699 to 812)	**OR 0.86** (0.63 to 1.17)	1053 (1 RCT)	⨁⨁◯◯ Low[c,d]	
Virological failure - 48 weeks	49 per 1,000	**46 per 1,000** (34 to 62)	**OR 0.93** (0.67 to 1.27)	3664 (4 RCTs)	⨁◯◯◯ Very low[b,c,d]	
Virological failure - 96 weeks	31 per 1,000	**41 per 1,000** (21 to 80)	**OR 1.33** (0.66 to 2.70)	1053 (1 RCT)	⨁⨁◯◯ Low[c,d]	
Failure with resistance - 48 weeks	200 per 1,000	**156 per 1,000** (54 to 373)	**OR 0.74** (0.23 to 2.38)	74 (4 RCTs)	⨁◯◯◯ Very low[b,c,d]	
Failure with resistance - 96 weeks	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 17.22** (0.95 to 312.93)	49 (1 RCT)	⨁⨁◯◯ Low[c,d]	
AE-driven discontinuation - 48 weeks	11 per 1,000	**23 per 1,000** (13 to 40)	**OR 2.21** (1.25 to 3.90)	3664 (4 RCTs)	⨁⨁◯◯ Low[b,d]	
AE-driven discontinuation - 96 weeks	6 per 1,000	**16 per 1,000** (3 to 67)	**OR 2.78** (0.61 to 12.60)	1053 (1 RCT)	⨁⨁◯◯ Low[c,d]	
Serious AE - 48 weeks	64 per 1,000	**65 per 1,000** (51 to 84)	**OR 1.03** (0.79 to 1.35)	3664 (4 RCTs)	⨁◯◯◯ Very low[b,c,d]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TAF/FTC + any 3rd agent	**Risk with TDF/FTC**				
Serious AE - 96 weeks	51 per 1,000	**66 per 1,000** (38 to 109)	**OR 1.30** (0.74 to 2.27)	1053 (1 RCT)	⨁⨁◯◯ Low[c,d]	
Drug-related serious AE - 48 weeks	2 per 1,000	**6 per 1,000** (2 to 20)	**OR 2.43** (0.70 to 8.45)	2458 (2 RCTs)	⨁◯◯◯ Very low[c,e,f]	
Drug-related serious AE - 96 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome
Grade 3/4 AE - 48 weeks	81 per 1,000	**108 per 1,000** (88 to 132)	**OR 1.36** (1.09 to 1.71)	3664 (4 RCTs)	⨁⨁◯◯ Low[b,d]	
Grade 3/4 AE - 96 weeks	154 per 1,000	**222 per 1,000** (169 to 287)	**OR 1.57** (1.12 to 2.21)	1053 (1 RCT)	⨁⨁⨁◯ Moderate[d]	
Drug-related grade 3/4 AE - 48 weeks	23 per 1,000	**37 per 1,000** (24 to 57)	**OR 1.65** (1.05 to 2.59)	2786 (2 RCTs)	⨁⨁◯◯ Low[d,g]	
Drug-related grade 3/4 AE - 96 weeks	60 per 1,000	**103 per 1,000** (64 to 159)	**OR 1.80** (1.08 to 2.97)	1053 (1 RCT)	⨁⨁⨁◯ Moderate[d]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Difference between groups in numbers with missing data for virological outcomes for ADVANCE and Mills 2015

b. ADVANCE had good generalisability but AMBER included >80% white patients and a comparatively small proportion of female or older (>50 years) participants or who had high viral loads; Mills 2015 enrolled relatively few women and Sax 2015 enrolled a small proportion of women or participants with advanced HIV disease, and excluded patients with chronic hepatitis B virus infection.

c. 95% Confidence interval spans 1

d. Some concerns (ADVANCE was an open label study)

e. I2 >60%

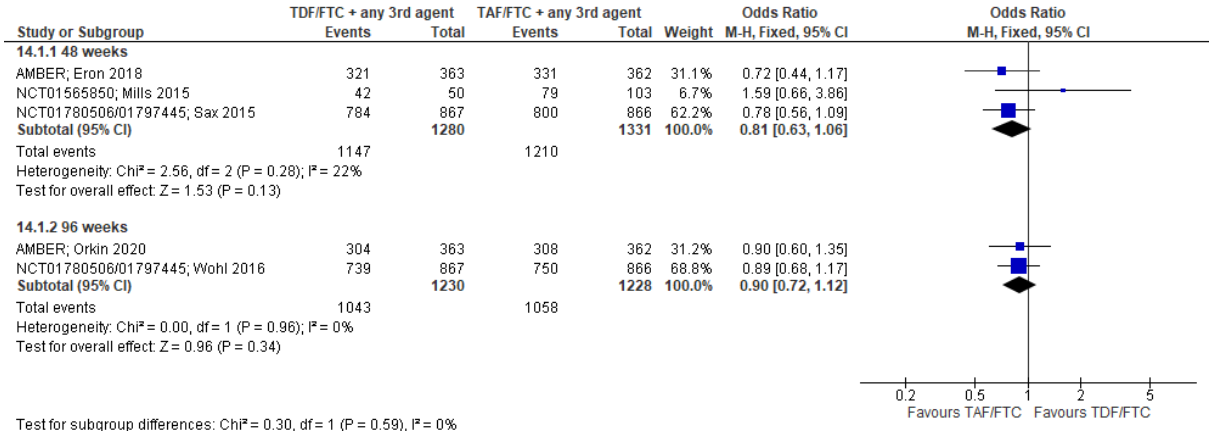
f. AMBER included >80% white patients and a comparatively small proportion of female or older (>50 years) participants or who had high viral loads and Sax 2015 enrolled a small proportion of women or participants with advanced HIV disease, and excluded patients with chronic hepatitis B virus infection.

g. ADVANCE had good generalisability but Sax 2015 enrolled a small proportion of women or participants with advanced HIV disease, and excluded patients with chronic hepatitis B virus infection.

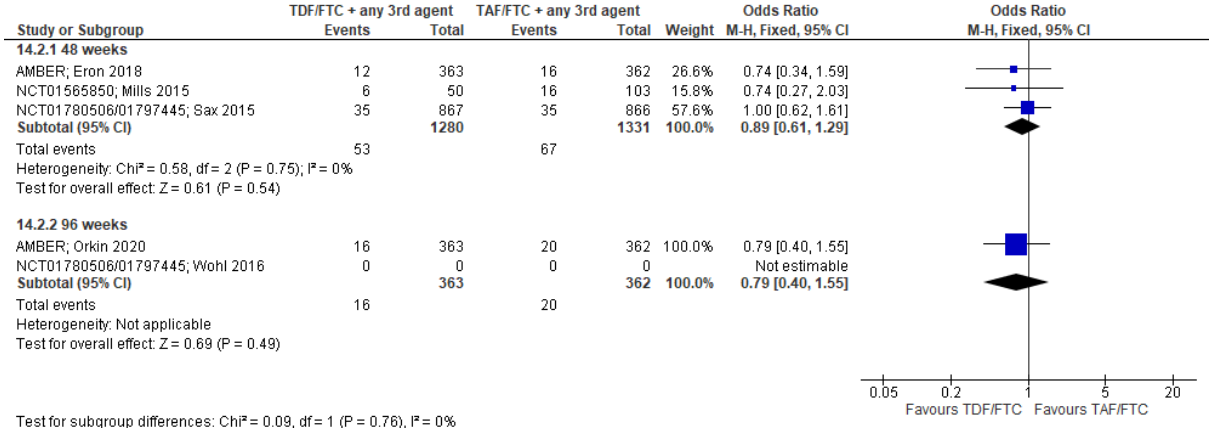
TDF/FTC vs TAF/FTC with any 3rd agent excluding ADVANCE and including week 96 data

Virological success, failure and missing data

Forest plot of comparison: 14 TDF/FTC vs TAF/FTC + any 3rd agent excluding ADVANCE, outcome: 14.1 Virological success.

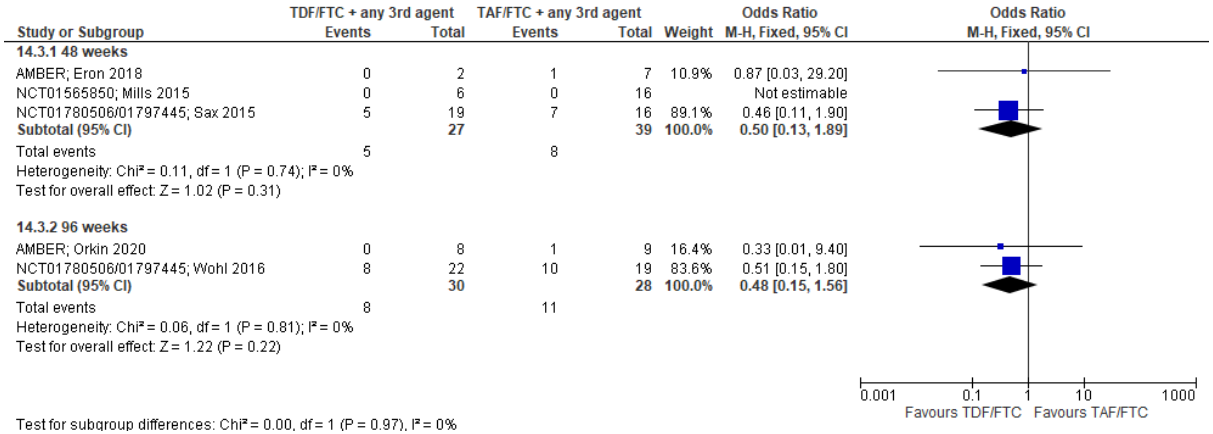


Forest plot of comparison: 14 TDF/FTC vs TAF/FTC + any 3rd agent excluding ADVANCE, outcome: 14.2 Virological failure.



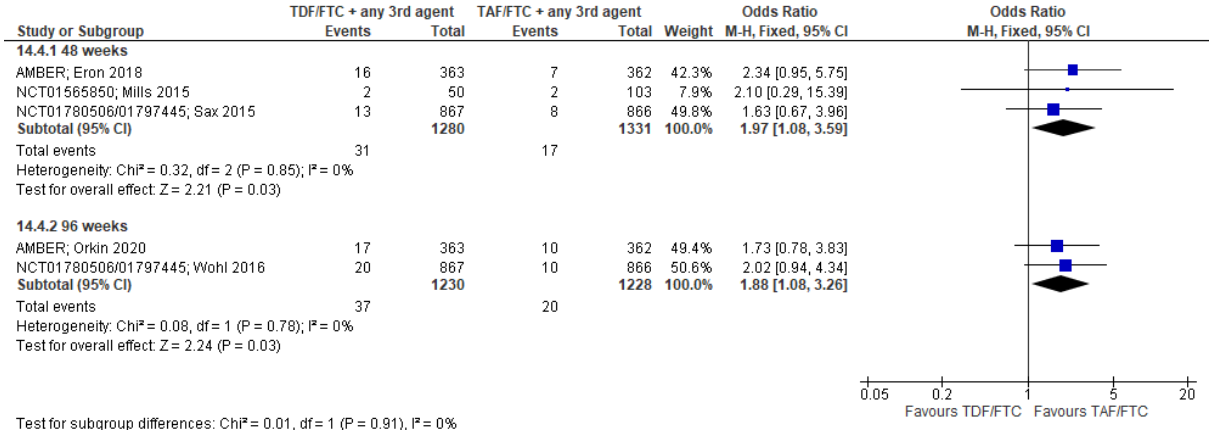
Failing with resistance

Forest plot of comparison: 14 TDF/FTC vs TAF/FTC + any 3rd agent excluding ADVANCE, outcome: 14.3 Failure with resistance.



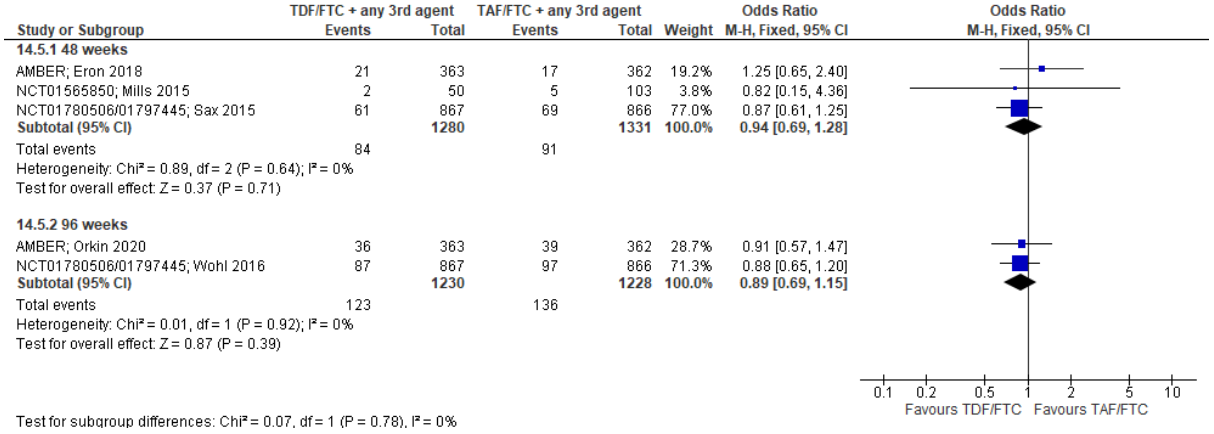
Adverse event (AE)-driven discontinuation

Forest plot of comparison: 14 TDF/FTC vs TAF/FTC + any 3rd agent excluding ADVANCE, outcome: 14.4 AE-driven discontinuation.



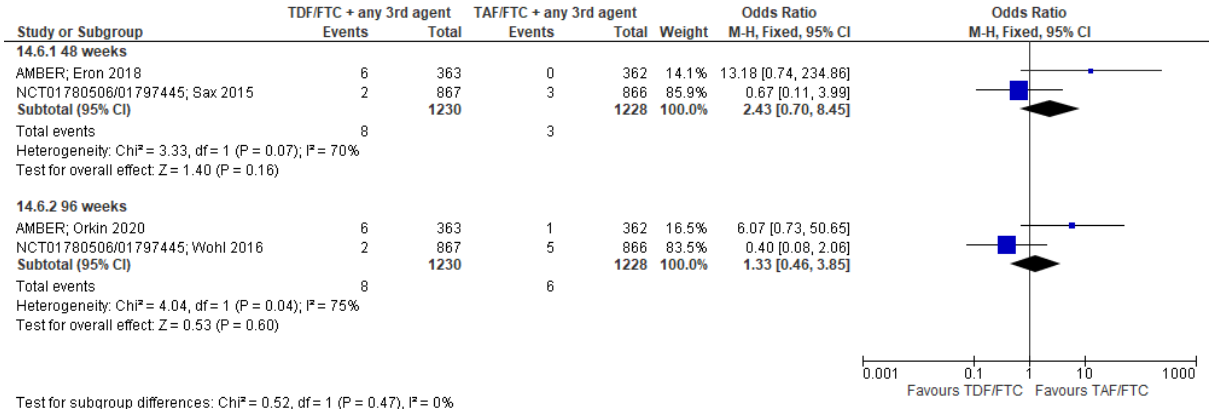
Serious adverse events

Forest plot of comparison: 14 TDF/FTC vs TAF/FTC + any 3rd agent excluding ADVANCE, outcome: 14.5 Serious AE.



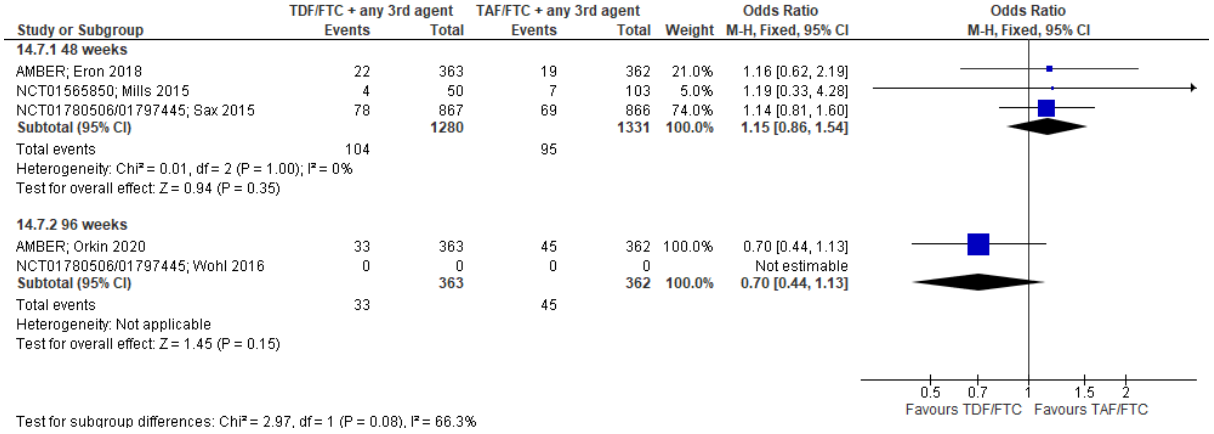
Drug-related SAE

Forest plot of comparison: 14 TDF/FTC vs TAF/FTC + any 3rd agent excluding ADVANCE, outcome: 14.6 Drug-related serious AE.



Grade 3/4 AE

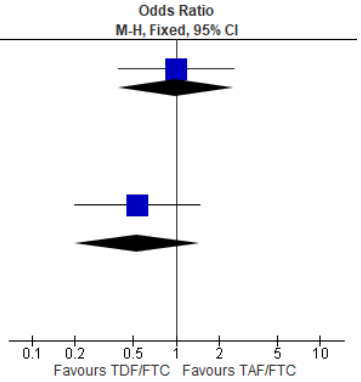
Forest plot of comparison: 14 TDF/FTC vs TAF/FTC + any 3rd agent excluding ADVANCE, outcome: 14.7 Grade 3/4 AE.



Drug-related Grade 3/4 AE

Forest plot of comparison: 14 TDF/FTC vs TAF/FTC + any 3rd agent excluding ADVANCE, outcome: 14.8 Drug-related grade 3/4 AE.

Study or Subgroup	TDF/FTC + any 3rd agent Events	Total	TAF/FTC + any 3rd agent Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
14.8.1 48 weeks						
NCT01780506/01797445; Sax 2015	9	867	9	866	100.0%	1.00 [0.39, 2.53]
Subtotal (95% CI)		**867**		**866**	**100.0%**	**1.00 [0.39, 2.53]**
Total events	9		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
14.8.2 96 weeks						
AMBER; Orkin 2020	6	363	11	362	100.0%	0.54 [0.20, 1.47]
NCT01780506/01797445; Wohl 2016	0	0	0	0		Not estimable
Subtotal (95% CI)		**363**		**362**	**100.0%**	**0.54 [0.20, 1.47]**
Total events	6		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.21 (P = 0.22)						



Test for subgroup differences: $Chi^2 = 0.79$, df = 1 (P = 0.37), $I^2 = 0\%$

GRADE

Summary of findings:

TDF/FTC compared to TAF/FTC + any 3rd agent excluding ADVANCE for HIV

Patient or population: HIV

Setting:

Intervention: TDF/FTC

Comparison: TAF/FTC + any 3rd agent excluding ADVANCE

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TAF/FTC + any 3rd agent excluding ADVANCE	**Risk with TDF/FTC**				
Virological success - 48 weeks	909 per 1,000	**890 per 1,000** (863 to 914)	**OR 0.81** (0.63 to 1.06)	2611 (3 RCTs)	⨁◯◯◯ Very low[a,b,c]	
Virological success - 96 weeks	862 per 1,000	**849 per 1,000** (818 to 875)	**OR 0.90** (0.72 to 1.12)	2458 (2 RCTs)	⨁⨁◯◯ Low[c,d]	
Virological failure - 48 weeks	50 per 1,000	**45 per 1,000** (31 to 64)	**OR 0.89** (0.61 to 1.29)	2611 (3 RCTs)	⨁◯◯◯ Very low[a,b,c]	
Virological failure - 96 weeks	55 per 1,000	**44 per 1,000** (23 to 83)	**OR 0.79** (0.40 to 1.55)	725 (2 RCTs)	⨁⨁◯◯ Low[c,e]	
Failure with resistance - 48 weeks	205 per 1,000	**114 per 1,000** (32 to 328)	**OR 0.50** (0.13 to 1.89)	66 (3 RCTs)	⨁⨁◯◯ Low[c,d]	

Summary of findings:

TDF/FTC compared to TAF/FTC + any 3rd agent excluding ADVANCE for HIV

Patient or population: HIV

Setting:

Intervention: TDF/FTC

Comparison: TAF/FTC + any 3rd agent excluding ADVANCE

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TAF/FTC + any 3rd agent excluding ADVANCE	**Risk with TDF/FTC**				
Failure with resistance - 96 weeks	393 per 1,000	**237 per 1,000** (88 to 502)	**OR 0.48** (0.15 to 1.56)	58 (2 RCTs)	⨁⨁◯◯ Low[c,d]	
AE-driven discontinuation - 48 weeks	13 per 1,000	**25 per 1,000** (14 to 44)	**OR 1.97** (1.08 to 3.59)	2611 (3 RCTs)	⨁⨁⨁◯ Moderate[b]	
AE-driven discontinuation - 96 weeks	16 per 1,000	**30 per 1,000** (18 to 51)	**OR 1.88** (1.08 to 3.26)	2458 (2 RCTs)	⨁⨁⨁◯ Moderate[d]	
Serious AE - 48 weeks	68 per 1,000	**65 per 1,000** (48 to 86)	**OR 0.94** (0.69 to 1.28)	2611 (3 RCTs)	⨁⨁◯◯ Low[b,c]	
Serious AE - 96 weeks	111 per 1,000	**100 per 1,000** (79 to 125)	**OR 0.89** (0.69 to 1.15)	2458 (2 RCTs)	⨁⨁◯◯ Low[c,d]	
Drug-related serious AE - 48 weeks	2 per 1,000	**6 per 1,000** (2 to 20)	**OR 2.43** (0.70 to 8.45)	2458 (2 RCTs)	⨁◯◯◯ Very low[c,d,f]	

Summary of findings:

TDF/FTC compared to TAF/FTC + any 3rd agent excluding ADVANCE for HIV

Patient or population: HIV

Setting:

Intervention: TDF/FTC

Comparison: TAF/FTC + any 3rd agent excluding ADVANCE

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TAF/FTC + any 3rd agent excluding ADVANCE	**Risk with TDF/FTC**				
Drug-related serious AE - 96 weeks	5 per 1,000	**6 per 1,000** (2 to 19)	**OR 1.33** (0.46 to 3.85)	2458 (2 RCTs)	⨁◯◯◯ Very low[c,d,f]	
Grade 3/4 AE - 48 weeks	71 per 1,000	**81 per 1,000** (62 to 106)	**OR 1.15** (0.86 to 1.54)	2611 (3 RCTs)	⨁⨁◯◯ Low[b,c]	
Grade 3/4 AE - 96 weeks	124 per 1,000	**90 per 1,000** (59 to 138)	**OR 0.70** (0.44 to 1.13)	725 (2 RCTs)	⨁⨁◯◯ Low[c,e]	
Drug-related grade 3/4 AE - 48 weeks	10 per 1,000	**10 per 1,000** (4 to 26)	**OR 1.00** (0.39 to 2.53)	1733 (1 RCT)	⨁⨁◯◯ Low[c,g]	
Drug-related grade 3/4 AE - 96 weeks	30 per 1,000	**17 per 1,000** (6 to 44)	**OR 0.54** (0.20 to 1.47)	725 (2 RCTs)	⨁⨁◯◯ Low[c,e]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

Summary of findings:

TDF/FTC compared to TAF/FTC + any 3rd agent excluding ADVANCE for HIV

Patient or population: HIV

Setting:

Intervention: TDF/FTC

Comparison: TAF/FTC + any 3rd agent excluding ADVANCE

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TAF/FTC + any 3rd agent excluding ADVANCE	**Risk with TDF/FTC**				

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Difference between groups numbers with missing data for virological outcomes in Mills 2015

b. AMBER included >80% white patients and a comparatively small proportion of female or older (>50 years) participants or who had high viral loads; Mills 2015 enrolled relatively few women and Sax 2015 enrolled a small proportion of women or participants with advanced HIV disease and excluded patients with chronic hepatitis B infection

c. 95% Confidence interval spans 1

d. AMBER included >80% white patients and a comparatively small proportion of female or older (>50 years) participants or who had high viral loads and Sax 2015 enrolled a small proportion of women or participants with advanced HIV disease and excluded patients with chronic hepatitis B infection

e. AMBER included >80% white patients and a comparatively small proportion of female or older (>50 years) participants or who had high viral loads

f. I^2 >60%

g. Sax 2015 enrolled a small proportion of women or participants with advanced HIV disease and excluded patients with chronic hepatitis B infection

9 ABC/3TC vs TAF/FTC with any 3rd agent

NCT02607930 data were published for week 48 results (Gallant 2017) and week 96 results (Wohl 2019).

Table 17. Key features of the included studies

Study name/ NCT number	Citation	Inclusion criteria	Exclusions	Population (n; demographics)	Intervention	Comparator	Outcomes
NCT02607930; GS-US-380-1489; 2015-004024-54 (EudraCT Number)	Gallant J, Lazzarin A, Mills A, Orkin C, Podzamczer D, Tebas P, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet (london, england). 2017;390(10107):2063-72.	HIV-1-infected adults (aged ≥18 years) who were previously untreated and had plasma HIV-1 RNA concentrations of 500 copies per mL or more, no hepatitis B virus infection, were HLA-B*5701-negative, had an eGFR of 50 mL/min or more (Cockcroft–Gault equation), and had no documented resistance	An opportunistic illness indicative of stage 3 HIV diagnosed within the 30 days prior to screening (refer to study protocol) Decompensated cirrhosis (e.g., ascites, encephalopathy, or variceal bleeding) Current alcohol or substance use judged by the Investigator to potentially interfere with subject study compliance Females who are pregnant (as confirmed	629 participants in 122 outpatient centres in nine countries in Europe, Latin America, and North America. B/F/TAF group (n=314); DTG/ABC/3TC group (n=315) Age (years) 31 (18–71); 32 (18–68) Female 29 (9%); 33 (10%) Male 285 (91%); 282 (90%) Race: White 180 (57%); 179 (57%) Black 114 (36%); 112 (36%) Asian 6 (2%); 10 (3%) American Indian or Alaska Native 2 (1%); 4 (1%) Native Hawaiian or Pacific Islander 1 (<1%); 2 (1%) Other 9 (3%); 8 (3%) Not permitted 2 (1%); 0 Hispanic or Latino 72 (23%); 65 (21%)	Dolutegravir, abacavir and lamivudine	Bictegravir, emtricitabine and tenofovir alafenamide	The primary outcome was the proportion of participants with plasma HIV-1 RNA < 50 copies per mL at week 48, as defined by the US Food and Drug Administration (FDA) snapshot algorithm. Additional prespecified efficacy endpoints included the proportion of participants with plasma HIV-1 RNA <50 copies

		to emtricitabine, tenofovir, abacavir, or lamivudine.	by positive serum pregnancy test) Females who are breastfeeding Chronic Hepatitis B Virus (HBV) infection	HIV disease status: Asymptomatic 286 (91%); 286 (91%) Symptomatic 16 (5%); 14 (4%) AIDS 12 (4%); 15 (5%) HIV risk factor: Heterosexual sex 61 (19%); 62 (20%) Homosexual sex 251 (80%); 250 (79%) Intravenous drug use 5 (2%); 4 (1%) HIV-1 RNA (log10 copies per mL) 4·42 (4·03–4·87); 4·51 (4·04–4·87) HIV-1 RNA >100 000 copies per mL 53 (17%); 50 (16%) CD4 count (cells per µL): 443 (299–590); 450 (324–608) <50: 7 (2%); 10 (3%) ≥50 to <200: 29 (9%); 22 (7%) ≥200 to <350: 69 (22%); 58 (18%) ≥350 to <500: 87 (28%); 91 (29%) ≥500: 122 (39%); 134 (43%) Creatinine clearance (mL/min)* 125·9 (107·7–146·3); 123·0 (107·0–144·3) Body-mass index (kg/m²) 25·1 (22·4–28·7); 24·9 (22·5–29·1) Data are median (IQR [range for age]) or n (%).			per mL at week 48 after imputation of missing-as-failure and missing-as-excluded values.

				B/F/TAF=bictegravir, emtricitabine, and tenofovir alafenamide. DTG/ABC/3TC=dolutegravir, abacavir, and lamivudine. *Estimated with the Cockcroft–Gault equation.			
	Wohl, DA; Yazdanpanah, Y; Baumgarten, A; Clarke, A; Thompson, MA; Brinson, C; Hagins, D; Ramgopal, MN; Antinori, A; Wei, X; Acosta, R; Collins, SE; Brainard, D; Martin, H. Bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. The lancet. HIV 2019; 6(6): e355-363. DOI: 10.1016/S2352-3018(19)30077-3. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01963192/full	As above	As above	As above	As above	As above	As above

Table . Comparisons included in this section

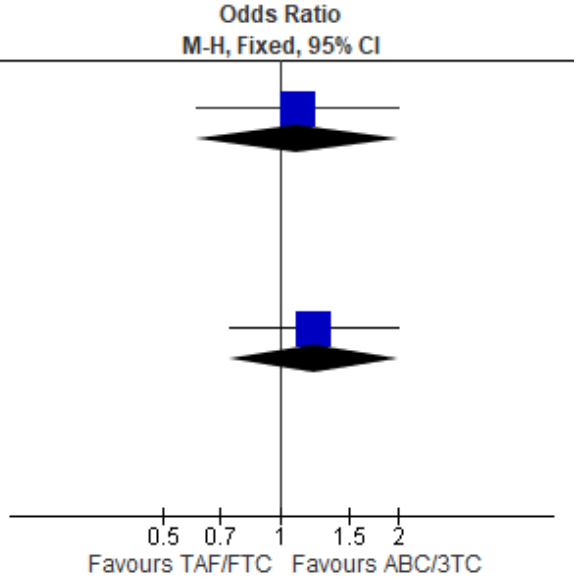
Study name/ NCT number	Intervention (ABC/3TC+ any 3rd agent)	Comparator (TAF/FTC + any 3rd agent)
NCT02607930; GS-US-380-1489; 2015-004024-54 (EudraCT Number)	Dolutegravir, abacavir and lamivudine	Bictegravir, emtricitabine and tenofovir alafenamide

Virological success, failure and missing data

Forest plot of comparison: 9 ABC/3TC vs TAF/FTC + any 3rd agent, outcome: 9.1 Virological success.

Study or Subgroup	ABC/3TC + any 3rd agent Events	Total	TAF/FTC + any 3rd agent Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
9.1.1 48 weeks						
NCT02607930; Gallant 2017	293	315	290	314	100.0%	1.10 [0.60, 2.01]
Subtotal (95% CI)		**315**		**314**	**100.0%**	**1.10 [0.60, 2.01]**
Total events	293		290			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
9.1.2 96 weeks						
NCT02607930; Wohl 2019	283	315	276	314	100.0%	1.22 [0.74, 2.00]
Subtotal (95% CI)		**315**		**314**	**100.0%**	**1.22 [0.74, 2.00]**
Total events	283		276			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						

Test for subgroup differences: $Chi^2 = 0.06$, df = 1 (P = 0.80), $I^2 = 0\%$



Forest plot of comparison: 9 ABC/3TC vs TAF/FTC + any 3rd agent, outcome: 9.2 Virological failure.

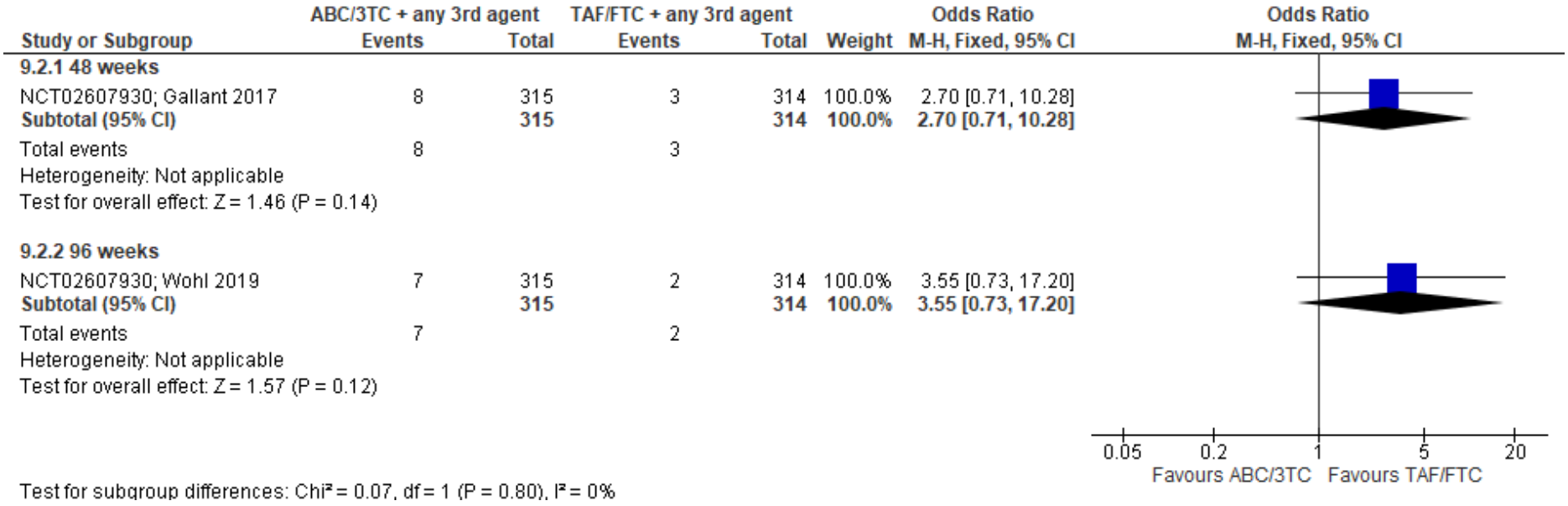


Figure 17. Success, failure and missing data at 48 weeks

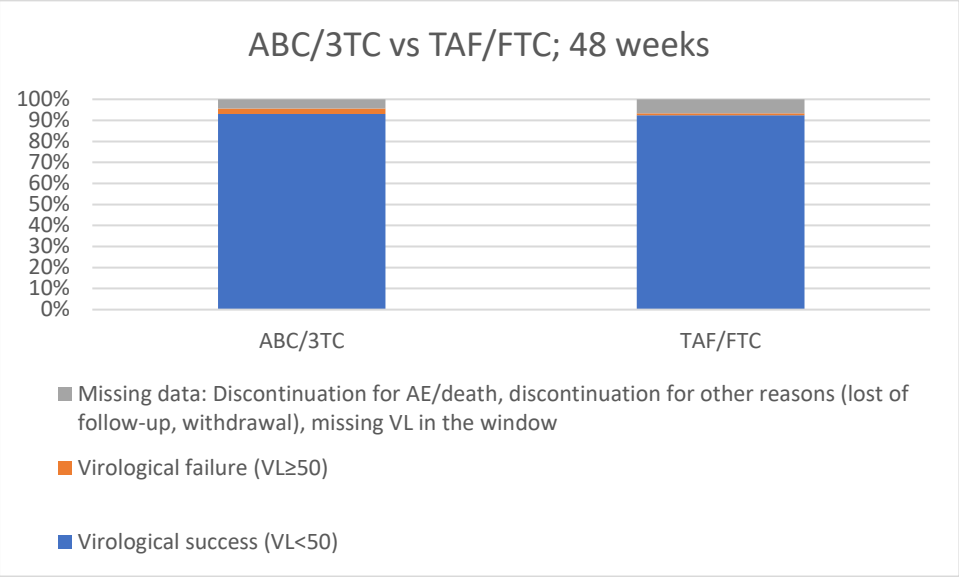
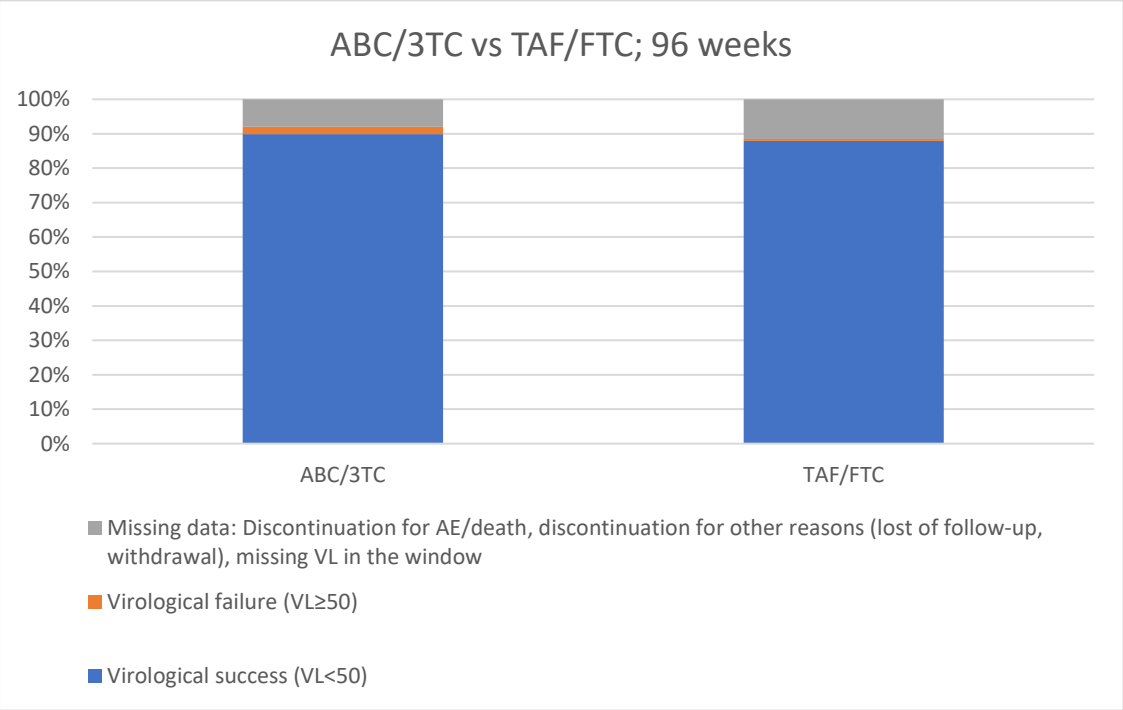


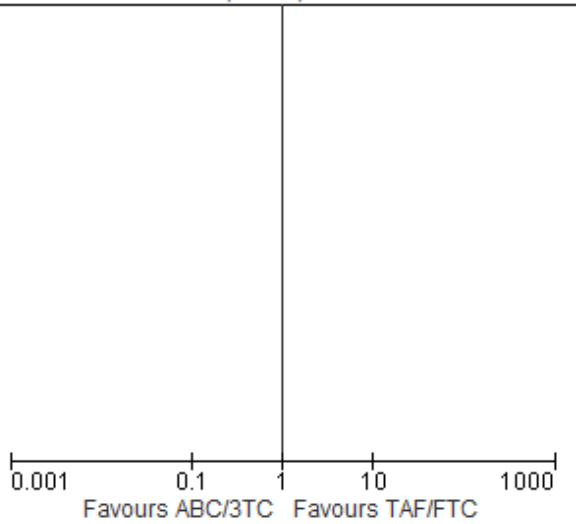
Figure 18. Success, failure and missing data at 96 weeks



Failing with resistance

Forest plot of comparison: 9 ABC/3TC vs TAF/FTC + any 3rd agent, outcome: 9.3 Failure with resistance.

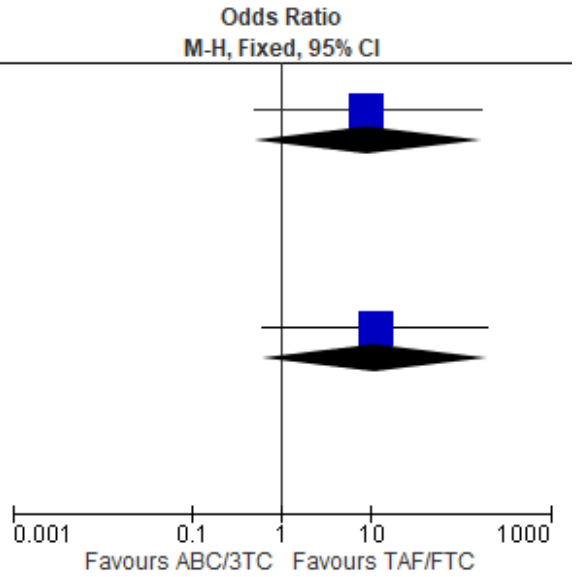
Study or Subgroup	ABC/3TC + any 3rd agent Events	Total	TAF/FTC + any 3rd agent Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
9.3.1 48 weeks						
NCT02607930; Gallant 2017	0	4	0	1		Not estimable
Subtotal (95% CI)		**4**		**1**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.3.2 96 weeks						
NCT02607930; Wohl 2019	0	5	0	0		Not estimable
Subtotal (95% CI)		**5**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Adverse event (AE)-driven discontinuation

Forest plot of comparison: 9 ABC/3TC vs TAF/FTC + any 3rd agent, outcome: 9.4 AE-driven discontinuation.

Study or Subgroup	ABC/3TC + any 3rd agent Events	Total	TAF/FTC + any 3rd agent Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
9.4.1 48 weeks						
NCT02607930; Gallant 2017	4	315	0	314	100.0%	9.09 [0.49, 169.48]
Subtotal (95% CI)		**315**		**314**	**100.0%**	**9.09 [0.49, 169.48]**
Total events	4		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						
9.4.2 96 weeks						
NCT02607930; Wohl 2019	5	315	0	314	100.0%	11.14 [0.61, 202.35]
Subtotal (95% CI)		**315**		**314**	**100.0%**	**11.14 [0.61, 202.35]**
Total events	5		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.63 (P = 0.10)						



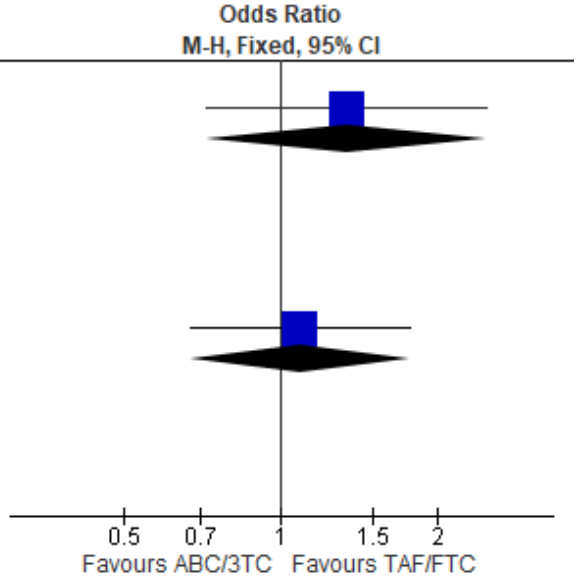
Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.92), $I^2 = 0\%$

Serious adverse events

Forest plot of comparison: 9 ABC/3TC vs TAF/FTC + any 3rd agent, outcome: 9.5 Serious AE.

Study or Subgroup	ABC/3TC + any 3rd agent Events	Total	TAF/FTC + any 3rd agent Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
9.5.1 48 weeks						
NCT02607930; Gallant 2017	25	315	19	314	100.0%	1.34 [0.72, 2.48]
Subtotal (95% CI)		**315**		**314**	**100.0%**	**1.34 [0.72, 2.48]**
Total events	25		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
9.5.2 96 weeks						
NCT02607930; Wohl 2019	39	315	36	314	100.0%	1.09 [0.67, 1.77]
Subtotal (95% CI)		**315**		**314**	**100.0%**	**1.09 [0.67, 1.77]**
Total events	39		36			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.35 (P = 0.72)						

Test for subgroup differences: Chi² = 0.26, df = 1 (P = 0.61), I² = 0%

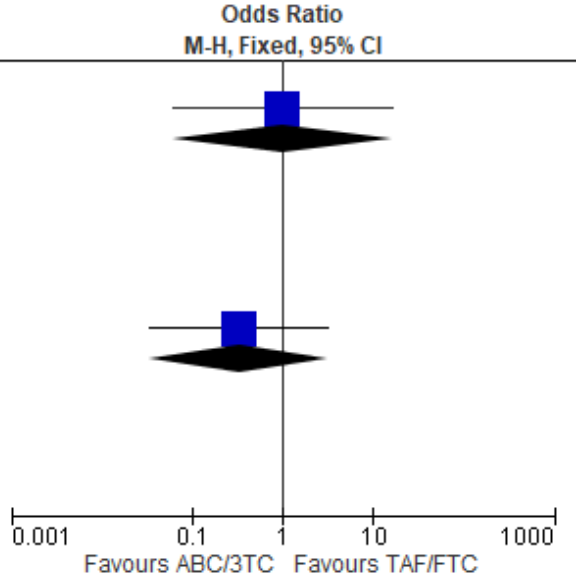


Drug-related SAE

Forest plot of comparison: 9 ABC/3TC vs TAF/FTC + any 3rd agent, outcome: 9.6 Drug-related serious AE.

Study or Subgroup	ABC/3TC + any 3rd agent Events	Total	TAF/FTC + any 3rd agent Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
9.6.1 48 weeks						
NCT02607930; Gallant 2017	1	315	1	314	100.0%	1.00 [0.06, 16.01]
Subtotal (95% CI)		**315**		**314**	**100.0%**	**1.00 [0.06, 16.01]**
Total events	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
9.6.2 96 weeks						
NCT02607930; Wohl 2019	1	315	3	314	100.0%	0.33 [0.03, 3.19]
Subtotal (95% CI)		**315**		**314**	**100.0%**	**0.33 [0.03, 3.19]**
Total events	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						

Test for subgroup differences: Chi² = 0.36, df = 1 (P = 0.55), I² = 0%

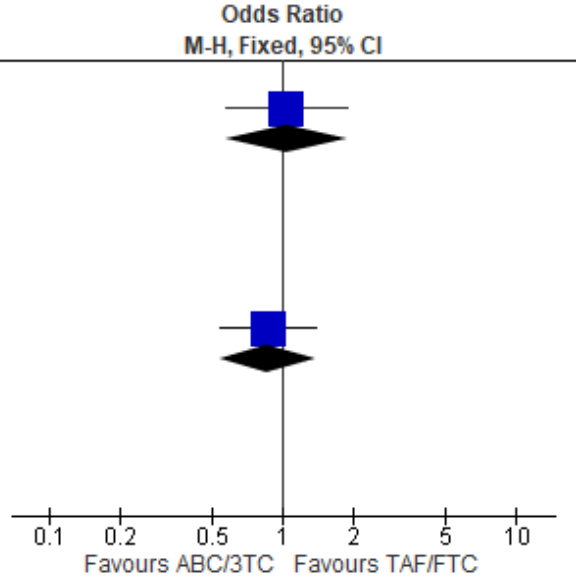


Grade 3/4 AE

Forest plot of comparison: 9 ABC/3TC vs TAF/FTC + any 3rd agent, outcome: 9.7 Grade 3/4 AE.

Study or Subgroup	ABC/3TC + any 3rd agent Events	Total	TAF/FTC + any 3rd agent Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
9.7.1 48 weeks						
NCT02607930; Gallant 2017	24	315	23	314	100.0%	1.04 [0.58, 1.89]
Subtotal (95% CI)		**315**		**314**	**100.0%**	**1.04 [0.58, 1.89]**
Total events	24		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						
9.7.2 96 weeks						
NCT02607930; Wohl 2019	37	315	42	314	100.0%	0.86 [0.54, 1.38]
Subtotal (95% CI)		**315**		**314**	**100.0%**	**0.86 [0.54, 1.38]**
Total events	37		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.54)						

Test for subgroup differences: $Chi^2 = 0.24$, df = 1 (P = 0.62), $I^2 = 0\%$

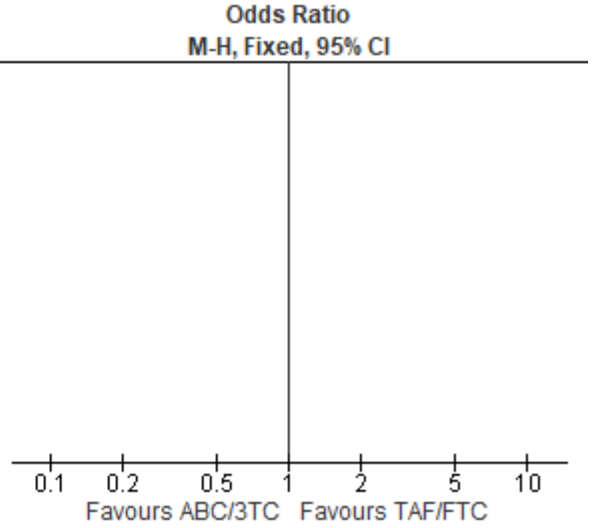


Drug-related Grade 3/4 AE

Forest plot of comparison: 9 ABC/3TC vs TAF/FTC + any 3rd agent, outcome: 9.8 Drug-related grade 3/4 AE.

Study or Subgroup	ABC/3TC + any 3rd agent Events	Total	TAF/FTC + any 3rd agent Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
9.8.1 48 weeks						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.8.2 96 weeks						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

Test for subgroup differences: Not applicable



GRADE table for critical outcomes

Outcomes	Anticipated absolute effects* (95% CI) Risk with TAF/FTC + any 3rd agent	Risk with ABC/3TC	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Virological success - 48 weeks	924 per 1,000	**930 per 1,000** (879 to 960)	**OR 1.10** (0.60 to 2.01)	629 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Virological success - 96 weeks	879 per 1,000	**899 per 1,000** (843 to 936)	**OR 1.22** (0.74 to 2.00)	629 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Virological failure - 48 weeks	10 per 1,000	**25 per 1,000** (7 to 90)	**OR 2.70** (0.71 to 10.28)	629 (1 RCT)	⨁⨁◯◯ Low[a,b]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TAF/FTC + any 3rd agent	**Risk with ABC/3TC**				
Virological failure - 96 weeks	6 per 1,000	**22 per 1,000** (5 to 99)	**OR 3.55** (0.73 to 17.20)	629 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Failure with resistance - 48 weeks	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	5 (1 RCT)	-	No events in either group
Failure with resistance - 96 weeks	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	5 (1 RCT)	-	No events in either group
AE-driven discontinuation - 48 weeks	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 9.09** (0.49 to 169.48)	629 (1 RCT)	⨁⨁◯◯ Low[a,b]	
AE-driven discontinuation - 96 weeks	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 11.14** (0.61 to 202.35)	629 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Serious AE - 48 weeks	61 per 1,000	**79 per 1,000** (44 to 138)	**OR 1.34** (0.72 to 2.48)	629 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Serious AE - 96 weeks	115 per 1,000	**124 per 1,000** (80 to 186)	**OR 1.09** (0.67 to 1.77)	629 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Drug-related serious AE - 48 weeks	3 per 1,000	**3 per 1,000** (0 to 49)	**OR 1.00** (0.06 to 16.01)	629 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Drug-related serious AE - 96 weeks	10 per 1,000	**3 per 1,000** (0 to 30)	**OR 0.33** (0.03 to 3.19)	629 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Grade 3/4 AE - 48 weeks	73 per 1,000	**76 per 1,000** (44 to 130)	**OR 1.04** (0.58 to 1.89)	629 (1 RCT)	⨁⨁◯◯ Low[a,b]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TAF/FTC + any 3rd agent	**Risk with ABC/3TC**				
Grade 3/4 AE - 96 weeks	134 per 1,000	**117 per 1,000** (77 to 176)	**OR 0.86** (0.54 to 1.38)	629 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Drug-related grade 3/4 AE - 48 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome
Drug-related grade 3/4 AE - 96 weeks	not pooled	not pooled	not pooled	(0 studies)	-	No studies reporting this outcome

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Small proportion of study participants with advanced HIV disease, and a small proportion of female participants.

b. 95% Confidence interval spans 1

Comparison of all studies for discontinuations for AE

Discontinuations due to AE (48 weeks)

	Regimen																	
Study	ABC, DTG, 3TC	ATV/r, FTC, TDF	BIC, FTC, TAF	COBI, DRV, FTC, TAF	COBI, DRV, FTC, TDF	COBI, EVG, FTC, TAF	COBI, EVG, FTC, TDF	DOR, FTC, TDF (or DOR, ABC, 3TC)	DOR, TDF, 3TC	DRV/r, FTC, TDF (or DRV/r, ABC, 3TC)	DTG, FTC, TAF	DTG, FTC, TDF	DTG, FTC, TDF (or DTG, ABC, 3TC)	DTG, 3TC	DTG, TDF, 3TC	EFV, FTC, TDF	EFV, TDF, 3TC	RAL, FTC, TDF (or RAL, ABC, 3TC)
ADVANCE											1/351 (0.3%)	0/351 (0%)				10/351 (2.8%)		
NAMSAL															0/310 (0%)		0/303 (0%)	
SINGLE	10/414 (2.4%)															42/419 (10.0%)		
GS-US-380-1489	4/315 (1.3%)		0/314 (0%)															
GS-US-380-1490			5/320 (1.6%)								1/325 (0.3%)							
ARIA	10/248 (4.0%)	17/247 (6.9%)																
FLAMINGO										9/242 (3.7%)			3/242 (1.2%)					
DRIVE-FORWARD								6/383 (1.6%)		12/383 (3.1%)								
DRIVE-AHEAD									11/364 (3.0%)							24/364 (6.6%)		
GEMINI												16/717 (2.2%)		15/716 (2.1%)				
SPRING-2													10/411 (2.4%)					10/411 (2.4%)
Sax 2015						8/866 (0.9%)	13/867 (1.5%)											
AMBER				7/362 (1.9%)	16/363 (4.4%)													
Mills 2015				2/103 (1.9%)	2/50 (4.0%)													
Total	24/977 (2.5%)	17/247 (6.9%)	5/634 (0.8%)	9/465 (1.9%)	18/413 (4.4%)	8/866 (0.9%)	13/867 (1.5%)	6/383 (1.6%)	11/364 (3.0%)	21/625 (3.4%)	2/676 (0.3%)	16/1068 (1.5%)	13/653 (2.0%)	15/716 (2.1%)	0/310 (0%)	76/1134 (6.7%)	0/303 (0%)	10/411 (2.4%)

Green: <1%; Yellow: 1-3%; Orange: 3-5%; Red: >5%

Appendix A. Search strategy

Medline

Limits: Humans, English, MEDLINE, from 2019/8/1 - 2021/6/30

Search strategy:

Search number	Query	Search Details	Results
10	#1 AND #8 AND #9	(("hiv"[MeSH Terms] OR "acquired immunodeficiency syndrome"[MeSH Terms]) AND ("humans"[MeSH Terms] AND "medline"[Filter] AND 2019/08/01:2021/06/30[Date - Publication] AND "english"[Language]) AND ((((("anti retroviral agents"[MeSH Terms] OR "antiretroviral therapy, highly active"[MeSH Terms] OR "HAART"[Title/Abstract] OR ("therap*"[Title/Abstract] OR "treat*"[Title/Abstract] OR "agent*"[Title/Abstract] OR "drug*"[Title/Abstract] OR "medication*"[Title/Abstract] OR "regime*"[Title/Abstract]) OR ("nrti*"[Title/Abstract] OR "nnrti*"[Title/Abstract]) OR "reverse transcriptase inhibitor*"[Title/Abstract] OR ("protease"[Title/Abstract] OR "integrase"[Title/Abstract])) AND ("humans"[MeSH Terms] AND "medline"[Filter] AND 2019/08/01:2021/06/30[Date - Publication] AND "english"[Language])) OR ((((("didanosine"[Title/Abstract] OR "lamivudine"[Title/Abstract] OR "nevirapine"[Title/Abstract] OR "stavudine"[Title/Abstract] OR "zidovudine"[Title/Abstract] OR "indinavir"[Title/Abstract] OR "nelfinavir"[Title/Abstract] OR "ritonavir"[Title/Abstract] OR "saquinavir"[Title/Abstract] OR "emtricitabine"[Title/Abstract] OR "rilpivirine"[Title/Abstract] OR "lopinavir"[Title/Abstract] OR "amprenavir"[Title/Abstract] OR "fosamprenavir"[Title/Abstract] OR "atazanavir"[Title/Abstract] OR "darunavir"[Title/Abstract] OR "tipranavir"[Title/Abstract] OR "maraviroc"[Title/Abstract] OR "enfuvirtide"[Title/Abstract] OR "raltegravir"[Title/Abstract] OR	702

"etravirine"[Title/Abstract] OR "abacavir"[Title/Abstract] OR "tenofovir"[Title/Abstract] OR "efavirenz"[Title/Abstract] OR "Kaletra"[Title/Abstract] OR "Combivir"[Title/Abstract] OR "Truvada"[Title/Abstract] OR "Atripla"[Title/Abstract] OR "Trizivir"[Title/Abstract] OR "Sustiva"[Title/Abstract]) AND ("humans"[MeSH Terms] AND "medline"[Filter] AND 2019/08/01:2021/06/30[Date - Publication] AND "english"[Language])) OR (("Stribild"[Title/Abstract] OR "eviplera"[Title/Abstract] OR "kivexa"[Title/Abstract] OR "elvitegravir"[Title/Abstract] OR "ziagen"[Title/Abstract] OR "emtriva"[Title/Abstract] OR "epivir"[Title/Abstract] OR "complera"[Title/Abstract] OR "retrovir"[Title/Abstract] OR "viread"[Title/Abstract] OR "stocrin"[Title/Abstract] OR "intelence"[Title/Abstract] OR "viramune"[Title/Abstract] OR "edurant"[Title/Abstract] OR "reyataz"[Title/Abstract] OR "prezista"[Title/Abstract] OR "telzir"[Title/Abstract] OR "norvir"[Title/Abstract] OR "aptivus"[Title/Abstract] OR "celsentri"[Title/Abstract] OR "dolutegravir"[Title/Abstract] OR "tivicay"[Title/Abstract] OR "vitekta"[Title/Abstract] OR "isentress"[Title/Abstract]) AND ("humans"[MeSH Terms] AND "medline"[Filter] AND 2019/08/01:2021/06/30[Date - Publication] AND "english"[Language])) OR (("Trii"[Title/Abstract] OR "epzicom"[Title/Abstract] OR "zerit"[Title/Abstract] OR "amdoxovir"[Title/Abstract] OR "videx"[Title/Abstract] OR "rescriptor"[Title/Abstract] OR "delavirdine"[Title/Abstract] OR "lersivirine"[Title/Abstract] OR "crixivan"[Title/Abstract] OR "invirase"[Title/Abstract] OR "lexiva"[Title/Abstract] OR "viracept"[Title/Abstract] OR "fuzeon"[Title/Abstract] OR "selzentry"[Title/Abstract] OR "cenicriviroc"[Title/Abstract] OR "ibalizumab"[Title/Abstract]) AND ("humans"[MeSH Terms] AND "medline"[Filter] AND 2019/08/01:2021/06/30[Date - Publication] AND "english"[Language])) OR (("Biktarvy"[Title/Abstract] OR "bictegravir"[Title/Abstract] OR "tenofovir alafenamide"[Title/Abstract] OR "doravirine"[Title/Abstract] OR "Pifeltro"[Title/Abstract] OR "Delstrigo"[Title/Abstract] OR "Descovy"[Title/Abstract] OR "cabotegravir"[Title/Abstract]) AND ("humans"[MeSH

		Terms] AND "medline"[Filter] AND 2019/08/01:2021/06/30[Date - Publication] AND "english"[Language]))) AND ("humans"[MeSH Terms] AND "medline"[Filter] AND 2019/08/01:2021/06/30[Date - Publication] AND "english"[Language]))) AND ("humans"[MeSH Terms] AND "medline"[Filter] AND 2019/08/01:2021/06/30[Date - Publication] AND "english"[Language])) AND (("firstline"[Title/Abstract] OR "first-line"[Title/Abstract] OR "first-line"[Title/Abstract] OR "initial"[Title/Abstract] OR "start*"[Title/Abstract] OR "begin*"[Title/Abstract] OR "initiat*"[Title/Abstract] OR "naive"[Title/Abstract] OR "naive"[Title/Abstract]) AND ("humans"[MeSH Terms] AND "medline"[Filter] AND 2019/08/01:2021/06/30[Date - Publication] AND "english"[Language]))) AND ((humans[Filter]) AND (medline[Filter]) AND (2019/8/1:2021/6/30[pdat]) AND (english[Filter]))	
9	firstline[Title/Abstract] OR first line[Title/Abstract] OR first-line[Title/Abstract] OR initial[Title/Abstract] OR start*[Title/Abstract] OR begin*[Title/Abstract] OR initiat*[Title/Abstract] OR naïve[Title/Abstract] OR naive[Title/Abstract]	("firstline"[Title/Abstract] OR "first-line"[Title/Abstract] OR "first-line"[Title/Abstract] OR "initial"[Title/Abstract] OR "start*"[Title/Abstract] OR "begin*"[Title/Abstract] OR "initiat*"[Title/Abstract] OR "naive"[Title/Abstract] OR "naive"[Title/Abstract]) AND ((humans[Filter]) AND (medline[Filter]) AND (2019/8/1:2021/6/30[pdat]) AND (english[Filter]))	89,354
8	#2 OR #7	((("anti retroviral agents"[MeSH Terms] OR "antiretroviral therapy, highly active"[MeSH Terms] OR "HAART"[Title/Abstract] OR ("therap*"[Title/Abstract] OR "treat*"[Title/Abstract] OR "agent*"[Title/Abstract] OR "drug*"[Title/Abstract] OR "medication*"[Title/Abstract] OR "regime*"[Title/Abstract]) OR ("nrti*"[Title/Abstract] OR "nnrti*"[Title/Abstract]) OR "reverse transcriptase inhibitor*"[Title/Abstract] OR ("protease"[Title/Abstract] OR "integrase"[Title/Abstract])) AND ("humans"[MeSH Terms] AND "medline"[Filter] AND 2019/08/01:2021/06/30[Date - Publication] AND "english"[Language])) OR ((((("didanosine"[Title/Abstract] OR "lamivudine"[Title/Abstract] OR	366,804

"nevirapine"[Title/Abstract] OR "stavudine"[Title/Abstract] OR "zidovudine"[Title/Abstract] OR "indinavir"[Title/Abstract] OR "nelfinavir"[Title/Abstract] OR "ritonavir"[Title/Abstract] OR "saquinavir"[Title/Abstract] OR "emtricitabine"[Title/Abstract] OR "rilpivirine"[Title/Abstract] OR "lopinavir"[Title/Abstract] OR "amprenavir"[Title/Abstract] OR "fosamprenavir"[Title/Abstract] OR "atazanavir"[Title/Abstract] OR "darunavir"[Title/Abstract] OR "tipranavir"[Title/Abstract] OR "maraviroc"[Title/Abstract] OR "enfuvirtide"[Title/Abstract] OR "raltegravir"[Title/Abstract] OR "etravirine"[Title/Abstract] OR "abacavir"[Title/Abstract] OR "tenofovir"[Title/Abstract] OR "efavirenz"[Title/Abstract] OR "Kaletra"[Title/Abstract] OR "Combivir"[Title/Abstract] OR "Truvada"[Title/Abstract] OR "Atripla"[Title/Abstract] OR "Trizivir"[Title/Abstract] OR "Sustiva"[Title/Abstract]) AND ("humans"[MeSH Terms] AND "medline"[Filter] AND 2019/08/01:2021/06/30[Date - Publication] AND "english"[Language])) OR (("Stribild"[Title/Abstract] OR "eviplera"[Title/Abstract] OR "kivexa"[Title/Abstract] OR "elvitegravir"[Title/Abstract] OR "ziagen"[Title/Abstract] OR "emtriva"[Title/Abstract] OR "epivir"[Title/Abstract] OR "complera"[Title/Abstract] OR "retrovir"[Title/Abstract] OR "viread"[Title/Abstract] OR "stocrin"[Title/Abstract] OR "intelence"[Title/Abstract] OR "viramune"[Title/Abstract] OR "edurant"[Title/Abstract] OR "reyataz"[Title/Abstract] OR "prezista"[Title/Abstract] OR "telzir"[Title/Abstract] OR "norvir"[Title/Abstract] OR "aptivus"[Title/Abstract] OR "celsentri"[Title/Abstract] OR "dolutegravir"[Title/Abstract] OR "tivicay"[Title/Abstract] OR "vitekta"[Title/Abstract] OR "isentress"[Title/Abstract]) AND ("humans"[MeSH Terms] AND "medline"[Filter] AND 2019/08/01:2021/06/30[Date - Publication] AND "english"[Language])) OR (("Trii"[Title/Abstract] OR "epzicom"[Title/Abstract] OR "zerit"[Title/Abstract] OR "amdoxovir"[Title/Abstract] OR "videx"[Title/Abstract] OR "rescriptor"[Title/Abstract] OR "delavirdine"[Title/Abstract] OR "lersivirine"[Title/Abstract] OR

		"crixivan"[Title/Abstract] OR "invirase"[Title/Abstract] OR "lexiva"[Title/Abstract] OR "viracept"[Title/Abstract] OR "fuzeon"[Title/Abstract] OR "selzentry"[Title/Abstract] OR "cenicriviroc"[Title/Abstract] OR "ibalizumab"[Title/Abstract]) AND ("humans"[MeSH Terms] AND "medline"[Filter] AND 2019/08/01:2021/06/30[Date - Publication] AND "english"[Language])) OR (("Biktarvy"[Title/Abstract] OR "bictegravir"[Title/Abstract] OR "tenofovir alafenamide"[Title/Abstract] OR "doravirine"[Title/Abstract] OR "Pifeltro"[Title/Abstract] OR "Delstrigo"[Title/Abstract] OR "Descovy"[Title/Abstract] OR "cabotegravir"[Title/Abstract]) AND ("humans"[MeSH Terms] AND "medline"[Filter] AND 2019/08/01:2021/06/30[Date - Publication] AND "english"[Language]))) AND ("humans"[MeSH Terms] AND "medline"[Filter] AND 2019/08/01:2021/06/30[Date - Publication] AND "english"[Language]))) AND ((humans[Filter]) AND (medline[Filter]) AND (2019/8/1:2021/6/30[pdat]) AND (english[Filter]))	
7	#3 OR #4 OR #5 OR #6	(((("didanosine"[Title/Abstract] OR "lamivudine"[Title/Abstract] OR "nevirapine"[Title/Abstract] OR "stavudine"[Title/Abstract] OR "zidovudine"[Title/Abstract] OR "indinavir"[Title/Abstract] OR "nelfinavir"[Title/Abstract] OR "ritonavir"[Title/Abstract] OR "saquinavir"[Title/Abstract] OR "emtricitabine"[Title/Abstract] OR "rilpivirine"[Title/Abstract] OR "lopinavir"[Title/Abstract] OR "amprenavir"[Title/Abstract] OR "fosamprenavir"[Title/Abstract] OR "atazanavir"[Title/Abstract] OR "darunavir"[Title/Abstract] OR "tipranavir"[Title/Abstract] OR "maraviroc"[Title/Abstract] OR "enfuvirtide"[Title/Abstract] OR "raltegravir"[Title/Abstract] OR "etravirine"[Title/Abstract] OR "abacavir"[Title/Abstract] OR "tenofovir"[Title/Abstract] OR "efavirenz"[Title/Abstract] OR "Kaletra"[Title/Abstract] OR "Combivir"[Title/Abstract] OR "Truvada"[Title/Abstract] OR "Atripla"[Title/Abstract] OR "Trizivir"[Title/Abstract] OR "Sustiva"[Title/Abstract]) AND ("humans"[MeSH Terms] AND "medline"[Filter]	2,060

AND 2019/08/01:2021/06/30[Date - Publication] AND "english"[Language])) OR (("Stribild"[Title/Abstract] OR "eviplera"[Title/Abstract] OR "kivexa"[Title/Abstract] OR "elvitegravir"[Title/Abstract] OR "ziagen"[Title/Abstract] OR "emtriva"[Title/Abstract] OR "epivir"[Title/Abstract] OR "complera"[Title/Abstract] OR "retrovir"[Title/Abstract] OR "viread"[Title/Abstract] OR "stocrin"[Title/Abstract] OR "intelence"[Title/Abstract] OR "viramune"[Title/Abstract] OR "edurant"[Title/Abstract] OR "reyataz"[Title/Abstract] OR "prezista"[Title/Abstract] OR "telzir"[Title/Abstract] OR "norvir"[Title/Abstract] OR "aptivus"[Title/Abstract] OR "celsentri"[Title/Abstract] OR "dolutegravir"[Title/Abstract] OR "tivicay"[Title/Abstract] OR "vitekta"[Title/Abstract] OR "isentress"[Title/Abstract]) AND ("humans"[MeSH Terms] AND "medline"[Filter] AND 2019/08/01:2021/06/30[Date - Publication] AND "english"[Language])) OR (("Trii"[Title/Abstract] OR "epzicom"[Title/Abstract] OR "zerit"[Title/Abstract] OR "amdoxovir"[Title/Abstract] OR "videx"[Title/Abstract] OR "rescriptor"[Title/Abstract] OR "delavirdine"[Title/Abstract] OR "lersivirine"[Title/Abstract] OR "crixivan"[Title/Abstract] OR "invirase"[Title/Abstract] OR "lexiva"[Title/Abstract] OR "viracept"[Title/Abstract] OR "fuzeon"[Title/Abstract] OR "selzentry"[Title/Abstract] OR "cenicriviroc"[Title/Abstract] OR "ibalizumab"[Title/Abstract]) AND ("humans"[MeSH Terms] AND "medline"[Filter] AND 2019/08/01:2021/06/30[Date - Publication] AND "english"[Language])) OR (("Biktarvy"[Title/Abstract] OR "bictegravir"[Title/Abstract] OR "tenofovir alafenamide"[Title/Abstract] OR "doravirine"[Title/Abstract] OR "Pifeltro"[Title/Abstract] OR "Delstrigo"[Title/Abstract] OR "Descovy"[Title/Abstract] OR "cabotegravir"[Title/Abstract]) AND ("humans"[MeSH Terms] AND "medline"[Filter] AND 2019/08/01:2021/06/30[Date - Publication] AND "english"[Language]))) AND ((humans[Filter]) AND (medline[Filter]) AND (2019/8/1:2021/6/30[pdat]) AND (english[Filter]))

6	Biktarvy[Title/Abstract] OR bictegravir[Title/Abstract] OR tenofovir alafenamide[Title/Abstract] OR doravirine[Title/Abstract] OR Pifeltro[Title/Abstract] OR Delstrigo[Title/Abstract] OR Descovy[Title/Abstract] OR cabotegravir[Title/Abstract]	("Biktarvy"[Title/Abstract] OR "bictegravir"[Title/Abstract] OR "tenofovir alafenamide"[Title/Abstract] OR "doravirine"[Title/Abstract] OR "Pifeltro"[Title/Abstract] OR "Delstrigo"[Title/Abstract] OR "Descovy"[Title/Abstract] OR "cabotegravir"[Title/Abstract]) AND ((humans[Filter]) AND (medline[Filter]) AND (2019/8/1:2021/6/30[pdat]) AND (english[Filter]))	219
5	Trii[Title/Abstract] OR epzicom[Title/Abstract] OR zerit[Title/Abstract] OR amdoxovir[Title/Abstract] OR videx[Title/Abstract] OR rescriptor[Title/Abstract] OR delavirdine[Title/Abstract] OR lersivirine[Title/Abstract] OR crixivan[Title/Abstract] OR invirase[Title/Abstract] OR lexiva[Title/Abstract] OR viracept[Title/Abstract] OR fuzeon[Title/Abstract] OR selzentry[Title/Abstract] OR cenicriviroc[Title/Abstract] OR ibalizumab[Title/Abstract]	("Trii"[Title/Abstract] OR "epzicom"[Title/Abstract] OR "zerit"[Title/Abstract] OR "amdoxovir"[Title/Abstract] OR "videx"[Title/Abstract] OR "rescriptor"[Title/Abstract] OR "delavirdine"[Title/Abstract] OR "lersivirine"[Title/Abstract] OR "crixivan"[Title/Abstract] OR "invirase"[Title/Abstract] OR "lexiva"[Title/Abstract] OR "viracept"[Title/Abstract] OR "fuzeon"[Title/Abstract] OR "selzentry"[Title/Abstract] OR "cenicriviroc"[Title/Abstract] OR "ibalizumab"[Title/Abstract]) AND ((humans[Filter]) AND (medline[Filter]) AND (2019/8/1:2021/6/30[pdat]) AND (english[Filter]))	25
4	Stribild[Title/Abstract] OR eviplera[Title/Abstract] OR kivexa[Title/Abstract] OR elvitegravir[Title/Abstract]	("Stribild"[Title/Abstract] OR "eviplera"[Title/Abstract] OR "kivexa"[Title/Abstract] OR "elvitegravir"[Title/Abstract] OR "ziagen"[Title/Abstract] OR "emtriva"[Title/Abstract] OR "epivir"[Title/Abstract] OR "complera"[Title/Abstract] OR "retrovir"[Title/Abstract] OR "viread"[Title/Abstract] OR	299

	OR ziagen[Title/Abstract] OR emtriva[Title/Abstract] OR epivir[Title/Abstract] OR complera[Title/Abstract] OR retrovir[Title/Abstract] OR viread[Title/Abstract] OR stocrin[Title/Abstract] OR intelence[Title/Abstract] OR viramune[Title/Abstract] OR edurant[Title/Abstract] OR reyataz[Title/Abstract] OR prezista[Title/Abstract] OR telzir[Title/Abstract] OR norvir[Title/Abstract] OR aptivus[Title/Abstract] OR celsentri[Title/Abstract] OR dolutegravir[Title/Abstract] OR tivicay[Title/Abstract] OR vitekta[Title/Abstract] OR isentress[Title/Abstract]	"stocrin"[Title/Abstract] OR "intelence"[Title/Abstract] OR "viramune"[Title/Abstract] OR "edurant"[Title/Abstract] OR "reyataz"[Title/Abstract] OR "prezista"[Title/Abstract] OR "telzir"[Title/Abstract] OR "norvir"[Title/Abstract] OR "aptivus"[Title/Abstract] OR "celsentri"[Title/Abstract] OR "dolutegravir"[Title/Abstract] OR "tivicay"[Title/Abstract] OR "vitekta"[Title/Abstract] OR "isentress"[Title/Abstract]) AND ((humans[Filter]) AND (medline[Filter]) AND (2019/8/1:2021/6/30[pdat]) AND (english[Filter]))	
3	didanosine[Title/Abstract] OR lamivudine[Title/Abstract] OR nevirapine[Title/Abstract] OR stavudine[Title/Abstract] OR zidovudine[Title/Abstract] OR indinavir[Title/Abstract] OR nelfinavir[Title/Abstract] OR ritonavir[Title/Abstract] OR saquinavir[Title/Abstract]	("didanosine"[Title/Abstract] OR "lamivudine"[Title/Abstract] OR "nevirapine"[Title/Abstract] OR "stavudine"[Title/Abstract] OR "zidovudine"[Title/Abstract] OR "indinavir"[Title/Abstract] OR "nelfinavir"[Title/Abstract] OR "ritonavir"[Title/Abstract] OR "saquinavir"[Title/Abstract] OR "emtricitabine"[Title/Abstract] OR "rilpivirine"[Title/Abstract] OR "lopinavir"[Title/Abstract] OR "amprenavir"[Title/Abstract] OR "fosamprenavir"[Title/Abstract] OR "atazanavir"[Title/Abstract] OR "darunavir"[Title/Abstract] OR "tipranavir"[Title/Abstract] OR "maraviroc"[Title/Abstract] OR	1,916

	OR emtricitabine[Title/Abstract] OR rilpivirine[Title/Abstract] OR lopinavir[Title/Abstract] OR amprenavir[Title/Abstract] OR fosamprenavir[Title/Abstract] OR atazanavir[Title/Abstract] OR darunavir[Title/Abstract] OR tipranavir[Title/Abstract] OR maraviroc[Title/Abstract] OR enfuvirtide[Title/Abstract] OR raltegravir[Title/Abstract] OR etravirine[Title/Abstract] OR abacavir[Title/Abstract] OR tenofovir[Title/Abstract] OR efavirenz[Title/Abstract] OR Kaletra[Title/Abstract] OR Combivir[Title/Abstract] OR Truvada[Title/Abstract] OR Atripla[Title/Abstract] OR Trizivir[Title/Abstract] OR Sustiva[Title/Abstract]	"enfuvirtide"[Title/Abstract] OR "raltegravir"[Title/Abstract] OR "etravirine"[Title/Abstract] OR "abacavir"[Title/Abstract] OR "tenofovir"[Title/Abstract] OR "efavirenz"[Title/Abstract] OR "Kaletra"[Title/Abstract] OR "Combivir"[Title/Abstract] OR "Truvada"[Title/Abstract] OR "Atripla"[Title/Abstract] OR "Trizivir"[Title/Abstract] OR "Sustiva"[Title/Abstract]) AND ((humans[Filter]) AND (medline[Filter]) AND (2019/8/1:2021/6/30[pdat]) AND (english[Filter]))	
2	((((((antiretroviral agents[MeSH Terms]) OR (highly active antiretroviral therapy[MeSH Terms])) OR (HAART[Title/Abstract])) OR	("anti retroviral agents"[MeSH Terms] OR "antiretroviral therapy, highly active"[MeSH Terms] OR "HAART"[Title/Abstract] OR "therap*"[Title/Abstract] OR "treat*"[Title/Abstract] OR "agent*"[Title/Abstract] OR "drug*"[Title/Abstract] OR "medication*"[Title/Abstract] OR "regime*"[Title/Abstract] OR "nrti*"[Title/Abstract] OR "nnrti*"[Title/Abstract] OR "reverse transcriptase	366,675

	(therap*[Title/Abstract] OR treat*[Title/Abstract] OR agent*[Title/Abstract] OR drug*[Title/Abstract] OR medication*[Title/Abstract] OR regime*[Title/Abstract])) OR (NRTI*[Title/Abstract] OR NNRTI*[Title/Abstract])) OR ("reverse transcriptase inhibitor*"[Title/Abstract])) OR (protease[Title/Abstract] OR integrase[Title/Abstract])	inhibitor*"[Title/Abstract] OR "protease"[Title/Abstract] OR "integrase"[Title/Abstract]) AND ((humans[Filter]) AND (medline[Filter]) AND (2019/8/1:2021/6/30[pdat]) AND (english[Filter]))	
1	("hiv"[MeSH Terms]) OR (aids[MeSH Terms])	("hiv"[MeSH Terms] OR "acquired immunodeficiency syndrome"[MeSH Terms]) AND ((humans[Filter]) AND (medline[Filter]) AND (2019/8/1:2021/6/30[pdat]) AND (english[Filter]))	4,004

Cochrane

Date Run: 01/06/2021

Search strategy:

ID	Search	Hits
#1	MeSH descriptor: [AIDS Serodiagnosis] explode all trees	102
#2	MeSH descriptor: [HIV Infections] explode all trees	12861
#3	MeSH descriptor: [HIV] explode all trees	3134
#4	MeSH descriptor: [HIV Long-Term Survivors] explode all trees	7
#5	#1 OR #2 OR #3 OR #4	13004
#6	(HIV or HIV1 or HIV2 or "human immun* deficien[*3]" or PLWH or AIDS near/3 virus or "acquired immun* deficien[*3]"):ti,ab,kw	27426
#7	(“human immunodeficiency virus” or “human immunedeficiency virus” or “human immuno-deficiency virus” or “human immune-deficiency virus” or “acquired immunodeficiency syndrome” or “acquired immunedeficiency syndrome” or “acquired immuno-deficiency syndrome” or “acquired immune-deficiency syndrome”):ti,ab,kw	13829
#8	#5 OR #6 OR #7	28894
#9	MeSH descriptor: [Anti-Retroviral Agents] explode all trees	4342
#10	MeSH descriptor: [Antiretroviral Therapy, Highly Active] this term only	1230
#11	(HAART or ((antiretroviral or anti-retroviral) near/3 (therap* or treat* or agent* or drug* or medication* or regime*)) or NRTI* or NNRTI*):ti,ab,kw	9426
#12	(((nucleoside or non-nucleoside or nonnucleoside) near/2 “reverse transcriptase inhibitor*”) or ((protease or integrase) near/1 inhibitor*) or ((anti-HIV or anti-aids) near/1 (drug* or agent* or therap* or treat* or agent* or regime*))):ti,ab,kw	6135

#13 #9 OR #10 OR #11 OR #12 12386

#14 ((didanosine or lamivudine or nevirapine or stavudine or zidovudine or indinavir or nelfinavir or ritonavir or saquinavir or emtricitabine or rilpivirine or lopinavir or amprenavir or fosamprenavir or atazanavir or darunavir or tipranavir or maraviroc or enfuvirtide or raltegravir or etravirine or abacavir or tenofovir or efavirenz or Kaletra or Combivir or Truvada or Atripla or Trizivir or Sustiva)):ti,ab,kw 10561

#15 ((Stribild or eviplera or kivexa or elvitegravir or ziagen or emtriva or epivir or complera or retrovir or viread or stocrin or intelence or viramune or edurant or reyataz or prezista or telzir or norvir or aptivus or celsentri or dolutegravir or tivicay or vitekta or isentress)):ti,ab,kw 1248

#16 ((Trii or epzicom or zerit or amdoxovir or videx or rescriptor or delavirdine or lersivirine or crixivan or invirase or lexiva or viracept or fuzeon or selzentry or cenicriviroc or ibalizumab)):ti,ab,kw 280

#17 ((Biktarvy or cictegravir or tenofovir alafenamide or doravirine or Pifeltro or Delstrigo or Descovy or cabotegravir)):ti,ab,kw 708

#18 #14 OR #15 OR #16 OR #17 10810

#19 #13 OR #18 17346

#20 (((firstline or first-line or initial or start* or begin*) near/2 (therap* or regim* or anti-retroviral* or antiretroviral* or agent* or drug* or HAART or ART or treat* or medication*))):ti,ab,kw 40736

#21 ((naïve)):ti,ab,kw 17774

#22 #20 OR #21 56435

#23 #5 AND #19 6988

#24 #23 AND #22 1726

#25 #24 with Cochrane Library publication date Between Aug 2019 and Jun 2021 245

HIV conferences

CROI 2020 (croi2020-boston-abstract-ebook.pdf (croiconference.org)) and 2021 (vCROI-2021-Abstract-eBook.pdf (croiconference.org)) (2020: n=38 and 2021: n=41)

IAS Abstract Archive (abstract-archive.org) for 2020 (2021 not until July Conferences (iasociety.org)); no pdf but archives searched (n=15)

EAC 2019 (EACS 2019 – Abstract Book (wiley.com)) (2021 not until October AIDS Conference London 2021 | 18th European AIDS Conference (eacs-conference2021.com)) (n=60)

HIV drug therapy Glasgow 2020 (HIV Glasgow – Virtual, 5–8 October 2020 (wiley.com) or HIV Glasgow – Virtual, 5–8 October 2020: Journal of the International AIDS Society: Vol 23, No S7 (wiley.com)) (n=34)

BHIVA/BASHH joint conference 2021 (AbstractBook2021.pdf (bhiva.org)) (2020 cancelled due to Covid-19 [Conference Abstracts (bhiva.org)]; virtual programme saved BHIVA Virtual Conference 2020) (n=7)

Appendix B. Risk of bias assessments for each study

3rd agent comparisons

The following tables show the risk of bias assessments for the studies using the Cochrane ROB 2.0 tool.

1 DOL vs EFV + any 2NRTI

		1. Biases arising from the randomisation process			
Study name/ NCT number		**1.1 Was the allocation sequence random?**	**1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?**	**1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?**	**Risk of bias judgement**
NCT03122262; ADVANCE	Judgement	Yes	Yes	No	Low
	Description	Electronically generated	Electronically generated	Baseline characteristics were balanced across the groups	
NCT02777229; New Antiretroviral and Monitoring Strategies in HIV-Infected Adults in Low-Income Countries (NAMSAL) ANRS 12313	Judgement	Yes	Yes	No	Low
	Description	Computer-generated	The randomization lists was produced prior to the start of the trial and will be given as confidential lists specifically to the person designed as responsible for the randomization center. This person was not directly involved in the trial and study team was blinded to randomization sequence.	Demographic and disease characteristics at baseline were well balanced between the two treatment groups	
NCT01263015; SINGLE	Judgement	Yes	Yes	No	Low
	Description	Randomization was performed in block sizes of six	Use of a central procedure	Demographic and disease characteristics at baseline were well balanced between the treatment groups	

		2. Bias due to deviations from the intended intervention (Effect of assignment to intervention)							
Study name/ NCT number		**2.1 Were participants aware of their assigned intervention during the trial?**	**2.2 Were carers and trial people delivering the interventions aware of the participants**	**2.3 If yes/ probably yes/no information to 2.1 or 2.2, were there deviations**	**2.4 If yes/ probably yes to 2.3, were these deviations likely to have**	**2.5 If yes/possibly yes/no information to 2.4 Were these deviations**	**2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?**	**2.7 If no/ probably no/no information to 2.6. Was there potential for a substantial**	**Risk of bias judgement**

			assigned intervention during the trial?	**from the intended intervention that arose because of the trial context?**	**affected the outcomes?**	**from intended intervention balanced between groups?**		**impact (on the result) of the failure to analyse the participants in the group to which they had been randomised?**	
NCT03122262; ADVANCE	Judgement	Yes	Yes	No information	NA	NA	Yes	NA	Some concerns
	Description	Open label	Open label	No details	NA	NA	Intention-to-treat analysis. After the testing for noninferiority, the treatment groups were compared for differences in efficacy. For these tests, an overall 1.7% significance level (P = 0.017) was used, to adjust for the three pairwise treatment comparisons being made.	NA	
NCT02777229; New Antiretroviral and Monitoring Strategies in HIV-Infected Adults in Low-Income Countries	Judgement	Yes	Yes	No information	NA	NA	Yes	NA	Some concerns
	Description	Open label	Open label	No details	NA	NA	Intention to treat	NA	

(NAMSAL) ANRS 12313									
NCT01263015; SINGLE	Judgement	No	No	NA	NA	NA	Yes	NA	Low
	Description	Double-blind	Double-blind	NA	NA	NA	Intention to treat	NA	

		2. Risk of bias due to deviations from the intended interventions (Effect of adhering to intervention)						
Study name/ NCT number		**2.1 Were participants aware of their assigned intervention during the trial?**	**2.2 Were carers and people delivering the interventions aware of the participants assigned intervention during the trial?**	**2.3 [If applicable] If yes/probably yes/ no information to 2.1 or 2.2 Were important non-protocol interventions balanced across intervention groups?**	**2.4 [If applicable] Were there failures in implementing the intervention that could have affected the outcome?**	**2.5 [If applicable] Was there non-adherence to the assigned intervention regimen that could have affected participant's outcomes?**	**2.6. If no/probably no/no information to 2.3, or yes probably yes/no information to 2.4 or 2.5 Was an appropriate analysis used to estimate the effect of adhering to the intervention?**	**Risk of bias judgement**
NCT03122262; ADVANCE	Judgement	Yes	Yes	No information	NA	NA	No information	Some concerns
	Description	Open label	Open label	No details	NA	NA	No details	
NCT02777229; New Antiretroviral and Monitoring Strategies in HIV-Infected Adults in Low-Income Countries (NAMSAL) ANRS 12313	Judgement	Yes	Yes	No information	NA	No	No information	Some concerns
	Description	Open label	Open label	No details	NA	Adherence to treatment was high on the basis of scores on a validated questionnaire. Adherence to treatment was similar in the two groups	No details	
NCT01263015; SINGLE	Judgement	No	No	NA	NA	No	NA	Low
	Description	Double-blind	Double-blind	NA	NA	Adherence to treatment was	NA	

						similar in the two study groups; 3 participants (2 participants in the DTG–ABC–3TC group and 1 in the EFV–TDF–FTC group) were excluded from the per-protocol population owing to an interruption of the study drug for more than 10% of the total time of treatment		

		3. Bias due to missing outcome data				
Study name/ NCT number		**3.1 Were outcome data available for all, or nearly all participants randomised?**	**3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?**	**3.3 If N/PN/NI to 3.2: Could missingness in the outcome depend on its true value?**	**3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?**	**Risk of bias judgement**
NCT03122262; ADVANCE	Judgement	No	No	Yes	Yes	High risk at week 48 for virological outcomes. Low at week 96 and other outcomes
	Description	By week 48, the number of patients who had discontinued treatment or who had missing data was 41 (12%) in the TAF-based group, 39	Differences in efficacy between the groups at 48 weeks were driven by a higher number of discontinuations in the standard-care	Differences in efficacy between the groups were driven by the number of discontinuations	Differences in efficacy between the groups were driven by the number of discontinuations	

		(11%) in the TDF-based group, and 55 (16%) in the standard-care group. By week 98 the numbers of patients who had no virological data, including those who discontinued for any reason other than lack of efficacy and those with missing data within the visit window were: 64/351 (18.2%) in the TAF-based group, 62 (17.7%) in the TDF-based group, 126/702 (17.9%) in the combined DOL groups and 78/351 (22.2%) in the standard-care group (not significantly different).	group than in the other two groups. In the per-protocol analysis, the percentage of patients with an HIV-1 RNA level <50 copies/mL was similar across the groups at week 48 (96% in the TAF-based group, 95% in the TDF-based group, and 96% in the standard-care group). At week 96, the difference in rate of missing data was similar between groups, and the differences in virological outcomes between groups were not significant either when missing data were classified as treatment failures or when missing were excluded.			
NCT02777229; New Antiretroviral and Monitoring Strategies in HIV-Infected Adults in Low-Income Countries (NAMSAL) ANRS 12313	Judgement	Yes	NA	NA	NA	Low risk
	Description	All included in intent to treat analysis. Of the 616 participants who underwent randomisation, 24 participants (4%) were excluded from the per-protocol analysis owing to deviations from the protocol	NA	NA	NA	

NCT01263015; SINGLE	Judgement	No	No	Yes	Yes	High risk at 48 and 96 weeks for virological outcomes; low for other outcomes
	Description	At weeks 48, virological outcome data were missing for 7.7% in the DOL group and 15.0% in the EFV group.	Overall differences in response (intention-to-treat analysis) were due primarily to discontinuations because of adverse events (10 of 414 participants [2%] in the DTG–ABC–3TC group and 42 of 419 [10%] in the EFV–TDF–FTC group). At week 96, differences in the virological response rate were driven by a lower rate of discontinuations due to AEs or deaths in the dolutegravir + abacavir/ lamivudine arm than in the efavirenz/tenofovir DF/emtricitabine arm: 13/414 (3%) vs. 48/419 (11%)	Differences in efficacy between the groups were driven by the number of discontinuations	Differences in efficacy between the groups were driven by the number of discontinuations	

		4. Bias in the measurement of the outcome					
Study name/ NCT number		**4.1 Was the method of measuring the outcome inappropriate?**	**4.2 Could measurement or ascertainment of the outcome have differed between**	**4.3 If N/PN to 4.1 and 4.2: Were outcome assessors aware of the intervention received by the**	**4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of**	**4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of**	**Risk of bias judgement**

			intervention groups?	**study participant?**	**intervention received?**	**intervention received?**	
NCT03122262; ADVANCE	Judgement	No	No	Yes	Probably no	NA	Low risk
	Description	The primary end point was the percentage of patients with an HIV-1 RNA level < 50 copies/mL at week 48. Secondary objectives were to evaluate additional viral-load thresholds, CD4 count changes, and side-effect profile and safety, including findings on physical examination, laboratory analyses, and dual-energy x-ray absorptiometry (DXA) scans.	Independent objective measurements as well as data from symptom screening, vital-signs measurement, symptom-directed physical examination, laboratory assessments, and multiple questionnaires, including a sleep questionnaire	Open label	Independent objective measurements as well as data from symptom screening, vital-signs measurement, symptom-directed physical examination, laboratory assessments, and multiple questionnaires, including a sleep questionnaire	NA	
NCT02777229; New Antiretroviral and Monitoring Strategies in HIV-Infected Adults in Low-Income Countries (NAMSAL) ANRS 12313	Judgement	No	No	Yes	No	NA	Low risk
	Description	The primary end point was the proportion of participants with a viral load of less than 50 copies/mL at week 48, on the basis of the Food and Drug Administration (FDA) snapshot algorithm	Objective measures at specified timepoints in protocol	Open label	Objective measures at specified timepoints in protocol	NA	
NCT01263015; SINGLE	Judgement	No	No	No	NA	NA	Low risk
	Description	The primary efficacy end point	The Abbott Real-Time HIV-1 assay	Double blind	NA	NA	

		was the proportion of participants with a plasma HIV-1 RNA level of less than 50 copies/mL at week 48, as determined with the use of the Snapshot algorithm from the Food and Drug Administration	was used to detect the plasma level of HIV-1 RNA (lower limit of detection, 40 copies/mL). CD4+ T-cell counts were assessed by means of flow cytometry in a central laboratory. Adverse events, serious adverse events, and laboratory measurements (including hematologic measurements, fasting lipid profile, and blood-chemistry profile) were assessed at each visit and graded according to the criteria of the Division of the Acquired Immunodeficiency Syndrome at the National Institute of Allergy and Infectious Diseases of the National Institutes of Health				

		5. Risk of bias in selection of the reported result	**RCT overall risk of bias**

Study name/ NCT number		**5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?**	**5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?**	**5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?**	**Risk of bias judgement**	
NCT03122262; ADVANCE	Judgement	Yes	No	No	Low	High risk at 48 weeks for virological outcomes Some concerns at 96 weeks (open label)
	Description	Pre-specified analysis plan	Pre-specified endpoints	Pre-specified analyses		
NCT02777229; New Antiretroviral and Monitoring Strategies in HIV-Infected Adults in Low-Income Countries (NAMSAL) ANRS 12313	Judgement	Yes	No	No	Low	Some concerns due to open label study
	Description	Pre-specified analysis plan	Pre-specified endpoints	Pre-specified analyses		
NCT01263015; SINGLE	Judgement	Yes	No	No	Low	High risk at 48 and 96 weeks for virological outcomes; low for other outcomes
	Description	Pre-specified analysis plan	Pre-specified endpoints	Pre-specified analyses		

SINGLE: Only 16% of the participants were women, and the proportion of participants with a CD4+ T-cell count of less than 200 per cubic millimeter was relatively low.

2 DOL vs BIC + any 2NRTI

		1. Biases arising from the randomisation process			
Study name/ NCT number		**1.1 Was the allocation sequence random?**	**1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?**	**1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?**	**Risk of bias judgement**
NCT02607930; GS-US-380-1489; 2015-004024-54 (EudraCT Number)	Judgement	Yes	Yes	No	Low
	Description	Computer-generated allocation sequence	Automated treatment assignment	Demographics and baseline characteristics were similar between groups	
NCT02607956; GS-US-380-1490; 2015-003988-10 (EudraCT Number)	Judgement	Yes	Yes	No	Low
	Description	Computer-generated allocation sequence	Study investigators identified eligibility of the participant, obtained a participant number, and received automated treatment assignment based on a randomisation sequence.	Demographics and baseline characteristics were balanced between the two treatment groups	

		2. Bias due to deviations from the intended intervention (Effect of assignment to intervention)							
Study name/ NCT number		**2.1 Were participants aware of their assigned intervention during the trial?**	**2.2 Were carers and trial people delivering the interventions aware of the participants assigned intervention during the trial?**	**2.3 If yes/ probably yes/no information to 2.1 or 2.2, were there deviations from the intended intervention that arose because of the trial context?**	**2.4 If yes/ probably yes to 2.3, were these deviations likely to have affected the outcomes?**	**2.5 If yes/ possibly yes/no information to 2.4 Were these deviations from intended intervention balanced between groups?**	**2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?**	**2.7 If no/ probably no/no information to 2.6. Was there potential for a substantial impact (on the result) of the failure to analyse the participants in the group to which they had been randomised?**	**Risk of bias judgement**
	Judgement	No	No	NA	NA	NA	Yes	NA	Low

NCT02607930; GS-US-380-1489; 2015-004024-54 (EudraCT Number)	Description	Investigators, participants, and study staff giving treatment, assessing outcomes, and collecting data were masked to group assignment.	Investigators, participants, and study staff giving treatment, assessing outcomes, and collecting data were masked to group assignment.	NA	NA	NA	Full analysis set (all participants who were randomly assigned and had received at least one dose of the study drug, regardless of whether they returned for post-baseline assessments)	NA	
NCT02607956; GS-US-380-1490; 2015-003988-10 (EudraCT Number)	Judgement	No	No	NA	NA	NA	Yes	NA	Low
	Description	Double-blind	Double-blind	NA	NA	NA	US FDA snapshot algorithm	NA	

		2. Risk of bias due to deviations from the intended interventions (Effect of adhering to intervention)						
Study name/ NCT number		**2.1 Were participants aware of their assigned intervention during the trial?**	**2.2 Were carers and people delivering the interventions aware of the participants assigned intervention during the trial?**	**2.3 [If applicable] If yes/probably yes/ no information to 2.1 or 2.2 Were important non-protocol interventions balanced across intervention groups?**	**2.4 [If applicable] Were there failures in implementing the intervention that could have affected the outcome?**	**2.5 [If applicable] Was there non-adherence to the assigned intervention regimen that could have affected participant's outcomes?**	**2.6. If no/probably no/no information to 2.3, or yes probably yes/no information to 2.4 or 2.5 Was an appropriate analysis used to estimate the effect of adhering to the intervention?**	**Risk of bias judgement**
	Judgement	No	No	NA	NA	NA	NA	Low

NCT02607930; GS-US-380-1489; 2015-004024-54 (EudraCT Number)	Description	Investigators, participants, and study staff giving treatment, assessing outcomes, and collecting data were masked to group assignment.	Investigators, participants, and study staff giving treatment, assessing outcomes, and collecting data were masked to group assignment.	NA	NA	NA	NA	
NCT02607956; GS-US-380-1490; 2015-003988-10 (EudraCT Number)	Judgement	No	No	NA	NA	NA	NA	Low
	Description	Double-blind	Double-blind	NA	NA	NA	NA	

		3. Bias due to missing outcome data				
Study name/ NCT number		**3.1 Were outcome data available for all, or nearly all participants randomised?**	**3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?**	**3.3 If N/PN/NI to 3.2: Could missingness in the outcome depend on its true value?**	**3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?**	**Risk of bias judgement**
NCT02607930; GS-US-380-1489; 2015-004024-54 (EudraCT Number)	Judgement	Yes	NA	NA	NA	Low
	Description	<6% missing values for virological outcomes at 48 weeks and <10% missing values for virological outcomes at 96 weeks	NA	NA	NA	
NCT02607956; GS-US-380-1490; 2015-003988-10 (EudraCT Number)	Judgement	Yes	NA	NA	NA	Low at 48 weeks; some concerns at 96 weeks
	Description	6.0% missing data for virological outcomes at 48 weeks and 11.2% missing data for virological	NA	NA	NA	

		outcomes at 96 weeks				

		4. Bias in the measurement of the outcome					
Study name/ NCT number		**4.1 Was the method of measuring the outcome inappropriate?**	**4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?**	**4.3 If N/PN to 4.1 and 4.2: Were outcome assessors aware of the intervention received by the study participant?**	**4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?**	**4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?**	**Risk of bias judgement**
NCT02607930; GS-US-380-1489; 2015-004024-54 (EudraCT Number)	Judgement	No	No	No	NA	NA	Low
	Description	Snapshot algorithm	Snapshot algorithm	Investigators, participants, and study staff giving treatment, assessing outcomes, and collecting data were masked to group assignment.	NA	NA	
NCT02607956; GS-US-380-1490; 2015-003988-10 (EudraCT Number)	Judgement	No	No	No	NA	NA	Low
	Description	Snapshot algorithm	Snapshot algorithm	Double-blind	NA	NA	

		5. Risk of bias in selection of the reported result				RCT overall risk of bias
Study name/ NCT number		**5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome**	**5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome**	**5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible**	**Risk of bias judgement**	

		data were available for analysis?	**measurements (e.g. scales, definitions, time points) within the outcome domain?**	**analyses of the data?**		
NCT02607930; GS-US-380-1489; 2015-004024-54 (EudraCT Number)	Judgement	Yes	No	No	Low	Low
	Description	Pre-specified analysis plan	Pre-specified endpoints	Pre-specified analyses		
NCT02607956; GS-US-380-1490; 2015-003988-10 (EudraCT Number)	Judgement	Yes	No	No	Low	Low at 48 weeks; some concerns at 96 weeks
	Description	Pre-specified analysis plan	Pre-specified endpoints	Pre-specified analyses		

Gallant 2017: small proportion of study participants with advanced HIV disease, and a small proportion of female participants.

Sax 2017: A small number of participants had advanced HIV-related immunosuppression (12%) or high HIV-1 RNA at baseline (19%), or were women.

3 DOL vs b/PI + any 2NRTI

		1. Biases arising from the randomisation process			
Study name/ NCT number		**1.1 Was the allocation sequence random?**	**1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?**	**1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?**	**Risk of bias judgement**
NCT01910402; ARIA	Judgement	Yes	Yes	No	Low
	Description	Validated computerised system	Randomisation and identifier code assignment were allocated centrally	Demographics and baseline characteristics were similar between groups	
NCT01449929; FLAMINGO	Judgement	Yes	Yes	No	Low
	Description	Computer-generated	Central interface	Baseline demographics and disease characteristics were similar between treatment groups	

		2. Bias due to deviations from the intended intervention (Effect of assignment to intervention)							
Study name/ NCT number		**2.1 Were participants aware of their assigned intervention during the trial?**	**2.2 Were carers and trial people delivering the interventions aware of the participants assigned intervention during the trial?**	**2.3 If yes/ probably yes/no information to 2.1 or 2.2, were there deviations from the intended intervention that arose because of the trial context?**	**2.4 If yes/ probably yes to 2.3, were these deviations likely to have affected the outcomes?**	**2.5 If yes/possibly yes/no information to 2.4 Were these deviations from intended intervention balanced between groups?**	**2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?**	**2.7 If no/ probably no/no information to 2.6. Was there potential for a substantial impact (on the result) of the failure to analyse the participants in the group to which they had been randomised?**	**Risk of bias judgement**
NCT01910402; ARIA	Judgement	Yes	Yes	Probably no	NA	NA	Yes	NA	Low
	Description	Open label	Open label	No details	NA	NA	US FDA snapshot algorithm for the intention-to-treat exposed (ITT-E) population,	NA	

							defined as all participants who received at least one dose of study medication.		
NCT01449929; FLAMINGO	Judgement	Yes	Yes	Probably no	NA	NA	Yes	NA	Low
	Description	Open label	Open label	No details	NA	NA	Snapshot algorithm	NA	

		2. Risk of bias due to deviations from the intended interventions (Effect of adhering to intervention)						
Study name/ NCT number		**2.1 Were participants aware of their assigned intervention during the trial?**	**2.2 Were carers and people delivering the interventions aware of the participants assigned intervention during the trial?**	**2.3 [If applicable] If yes/probably yes/ no information to 2.1 or 2.2 Were important non-protocol interventions balanced across intervention groups?**	**2.4 [If applicable] Were there failures in implementing the intervention that could have affected the outcome?**	**2.5 [If applicable] Was there non-adherence to the assigned intervention regimen that could have affected participant's outcomes?**	**2.6. If no/probably no/no information to 2.3, or yes probably yes/no information to 2.4 or 2.5 Was an appropriate analysis used to estimate the effect of adhering to the intervention?**	**Risk of bias judgement**
NCT01910402; ARIA	Judgement	Yes	Yes	NA	NA	NA	NA	Some concerns
	Description	Open label	Open label	NA	NA	NA	NA	
NCT01449929; FLAMINGO	Judgement	Yes	Yes	NA	NA	NA	NA	Some concerns
	Description	Open label	Open label	NA	NA	NA	NA	

		3. Bias due to missing outcome data

Study name/ NCT number		**3.1 Were outcome data available for all, or nearly all participants randomised?**	**3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?**	**3.3 If N/PN/NI to 3.2: Could missingness in the outcome depend on its true value?**	**3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?**	**Risk of bias judgement**
NCT01910402; ARIA	Judgement	No	No	Yes	Yes	High risk
	Description	13.5% missing data for virological outcomes	The ARIA study reported superiority primarily driven by the lower rates of adverse-event-related discontinuations and virological non-response in the dolutegravir group.	Open label	Open label	
NCT01449929; FLAMINGO	Judgement	No	No	Yes	Yes	High risk
	Description	7% missing data for virological outcomes	The FLAMINGO study reported that discontinuation due to adverse events or stopping criteria at 48 weeks was less frequent for dolutegravir (four [2%] patients) than for darunavir plus ritonavir (ten [4%] patients) and contributed to the difference in response rates. This study also reported that part of the difference in the virological response rates at 96 weeks was driven by a higher percentage of discontinuations for other reasons (e.g., lost to follow-up) in the darunavir plus	Open label	Open label	

			ritonavir group than in the dolutegravir group.			

		4. Bias in the measurement of the outcome					
Study name/ NCT number		**4.1 Was the method of measuring the outcome inappropriate?**	**4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?**	**4.3 If N/PN to 4.1 and 4.2: Were outcome assessors aware of the intervention received by the study participant?**	**4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?**	**4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?**	**Risk of bias judgement**
NCT01910402; ARIA	Judgement	No	No	Yes	No	NA	Low
	Description	Snapshot algorithm	Snapshot algorithm	Open label	Objective outcome	NA	
NCT01449929; FLAMINGO	Judgement	No	No	Yes	No	NA	Low
	Description	Snapshot algorithm	Snapshot algorithm	Open label	Objective outcome	NA	

		5. Risk of bias in selection of the reported result				RCT overall risk of bias
Study name/ NCT number		**5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before**	**5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible**	**5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible**	**Risk of bias judgement**	

		unblinded outcome data were available for analysis?	**outcome measurements (e.g. scales, definitions, time points) within the outcome domain?**	**analyses of the data?**		
NCT01910402; ARIA	Judgement	Yes	No	No	Low	High risk
	Description	Pre-specified analysis plan	Pre-specified endpoints	Pre-specified analyses		
NCT01449929; FLAMINGO	Judgement	Yes	No	No	Low	High risk
	Description	Pre-specified analysis plan	Pre-specified endpoints	Pre-specified analyses		

ARIA: women only

FLAMINGO: Low number of non-white, female, co-infected (HIV and hepatitis B or HIV and hepatitis C) patients or patients with advanced disease were enrolled

4 DOR vs b/PI + any 2NRTI

		1. Biases arising from the randomisation process			
Study name/ NCT number		**1.1 Was the allocation sequence random?**	**1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?**	**1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?**	**Risk of bias judgement**
NCT02275780; DRIVE-FORWARD; MK-1439-018	Judgement	Yes	Yes	No	Low
	Description	Interactive voice and web response system	Interactive voice and web response system	Demographics and baseline characteristics were balanced between the two treatment groups	

		2. Bias due to deviations from the intended intervention (Effect of assignment to intervention)							
Study name/ NCT number		**2.1 Were participants aware of their**	**2.2 Were carers and trial people delivering the**	**2.3 If yes/ probably yes/no information to**	**2.4 If yes/ probably yes to 2.3, were these**	**2.5 If yes/ possibly yes/no information**	**2.6 Was an appropriate analysis used to estimate**	**2.7 If no/ probably no/no information to**	**Risk of bias judgement**

		assigned intervention during the trial?	interventions aware of the participants assigned intervention during the trial?	2.1 or 2.2, were there deviations from the intended intervention that arose because of the trial context?	deviations likely to have affected the outcomes?	to 2.4 Were these deviations from intended intervention balanced between groups?	the effect of assignment to intervention?	2.6. Was there potential for a substantial impact (on the result) of the failure to analyse the participants in the group to which they had been randomised?	
NCT02275780; DRIVE-FORWARD; MK-1439-018	Judgement	No	No	NA	NA	NA	Yes	NA	Low
	Description	Double-blind	Double-blind	NA	NA	NA	US FDA snapshot algorithm	NA	

		2. Risk of bias due to deviations from the intended interventions (Effect of adhering to intervention)						
Study name/ NCT number		2.1 Were participants aware of their assigned intervention during the trial?	2.2 Were carers and people delivering the interventions aware of the participants assigned intervention during the trial?	2.3 [If applicable] If yes/probably yes/ no information to 2.1 or 2.2 Were important non-protocol interventions balanced across intervention groups?	2.4 [If applicable] Were there failures in implementing the intervention that could have affected the outcome?	2.5 [If applicable] Was there non-adherence to the assigned intervention regimen that could have affected participant's outcomes?	2.6. If no/probably no/no information to 2.3, or yes probably yes/no information to 2.4 or 2.5 Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Risk of bias judgement
NCT02275780; DRIVE-FORWARD; MK-1439-018	Judgement	No	No	NA	NA	NA	NA	Low
	Description	Double-blind	Double-blind	NA	NA	NA	NA	

		3. Bias due to missing outcome data

Study name/ NCT number		3.1 Were outcome data available for all, or nearly all participants randomised?	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	3.3 If N/PN/NI to 3.2: Could missingness in the outcome depend on its true value?	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Risk of bias judgement
NCT02275780; DRIVE-FORWARD; MK-1439-018	Judgement	Yes	NA	NA	NA	Low at 48 weeks; some concerns at 96 weeks
	Description	6.0% missing data for virological outcomes at week 48 and 11.8% missing data for virological outcomes at week 96	NA	NA	NA	

		4. Bias in the measurement of the outcome					
Study name/ NCT number		4.1 Was the method of measuring the outcome inappropriate?	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	4.3 If N/PN to 4.1 and 4.2: Were outcome assessors aware of the intervention received by the study participant?	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Risk of bias judgement
NCT02275780; DRIVE-FORWARD; MK-1439-018	Judgement	No	No	No	NA	NA	Low
	Description	Snapshot algorithm	Snapshot algorithm	Double-blind	NA	NA	

		5. Risk of bias in selection of the reported result				RCT overall risk of bias
Study name/ NCT number		5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that	5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from	Risk of bias judgement	

		was finalized before unblinded outcome data were available for analysis?	**multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?**	**multiple eligible analyses of the data?**		
NCT02275780; DRIVE-FORWARD; MK-1439-018	Judgement	Yes	No	No	Low	Low at 48 weeks; some concerns at 96 weeks
	Description	Pre-specified analysis plan	Pre-specified endpoints	Pre-specified analyses		

Molina 2018: low number of women (121 [16%]) and participants aged older than 65 years (1%) enrolled in the trial.

5 DOR vs EFV + any 2NRTI

		1. Biases arising from the randomisation process			
Study name/ NCT number		**1.1 Was the allocation sequence random?**	**1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?**	**1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?**	**Risk of bias judgement**
NCT02403674; DRIVE-AHEAD; MK-1439A Protocol 021	Judgement	Yes	Probably yes	No	Low
	Description	No details	No details	Demographics and baseline characteristics were generally similar between the treatment groups	

		2. Bias due to deviations from the intended intervention (Effect of assignment to intervention)							
Study name/ NCT number		**2.1 Were participants aware of their assigned intervention during the trial?**	**2.2 Were carers and trial people delivering the interventions aware of the participants assigned intervention during the trial?**	**2.3 If yes/ probably yes/no information to 2.1 or 2.2, were there deviations from the intended intervention that arose because of the trial context?**	**2.4 If yes/ probably yes to 2.3, were these deviations likely to have affected the outcomes?**	**2.5 If yes/ possibly yes/no information to 2.4 Were these deviations from intended intervention balanced between groups?**	**2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?**	**2.7 If no/ probably no/no information to 2.6. Was there potential for a substantial impact (on the result) of the failure to analyse the participants in the group to which they had been randomised?**	**Risk of bias judgement**
NCT02403674; DRIVE-AHEAD; MK-1439A Protocol 021	Judgement	No	No	NA	NA	NA	Yes	NA	Low
	Description	Double-blind	Double-blind	NA	NA	NA	Snapshot algorithm	NA	

		2. Risk of bias due to deviations from the intended interventions (Effect of adhering to intervention)						
Study name/ NCT number		**2.1 Were participants**	**2.2 Were carers and people**	**2.3 [If applicable] If**	**2.4 [If applicable]**	**2.5 [If applicable]**	**2.6. If no/probably**	**Risk of bias judgement**

		aware of their assigned intervention during the trial?	delivering the interventions aware of the participants assigned intervention during the trial?	yes/probably yes/ no information to 2.1 or 2.2 Were important non-protocol interventions balanced across intervention groups?	Were there failures in implementing the intervention that could have affected the outcome?	Was there non-adherence to the assigned intervention regimen that could have affected participant's outcomes?	no/no information to 2.3, or yes probably yes/no information to 2.4 or 2.5 Was an appropriate analysis used to estimate the effect of adhering to the intervention?	
NCT02403674; DRIVE-AHEAD; MK-1439A Protocol 021	Judgement	No	No	NA	NA	NA	NA	Low
	Description	Double-blind	Double-blind	NA	NA	NA	NA	

		3. Bias due to missing outcome data				
Study name/ NCT number		3.1 Were outcome data available for all, or nearly all participants randomised?	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	3.3 If N/PN/NI to 3.2: Could missingness in the outcome depend on its true value?	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Risk of bias judgement
NCT02403674; DRIVE-AHEAD; MK-1439A Protocol 021	Judgement	Yes	No	Yes	Yes	High risk
	Description	7.0% missing data for virological outcomes at week 48 and 10.9% missing data for virological outcomes at week 96	Rates of discontinuations for AEs differed between groups	Rates of discontinuations for AEs differed between groups	Rates of discontinuations for AEs differed between groups	

		4. Bias in the measurement of the outcome					
Study name/ NCT number		4.1 Was the method of measuring the outcome inappropriate?	4.2 Could measurement or ascertainment of the outcome have differed	4.3 If N/PN to 4.1 and 4.2: Were outcome assessors aware of the	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was	Risk of bias judgement

			between intervention groups?	**intervention received by the study participant?**	**influenced by knowledge of intervention received?**	**influenced by knowledge of intervention received?**	
NCT02403674; DRIVE-AHEAD; MK-1439A Protocol 021	Judgement	No	No	No	No	NA	High risk
	Description	Snapshot algorithm	Snapshot algorithm	Double-blind	Independent objective measurements	NA	

		5. Risk of bias in selection of the reported result				**RCT overall risk of bias**
Study name/ NCT number		**5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?**	**5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?**	**5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?**	**Risk of bias judgement**	
NCT02403674; DRIVE-AHEAD; MK-1439A Protocol 021	Judgement	Yes	No	No	Low	Low at 48 weeks; some concerns at 96 weeks
	Description	Pre-specified analysis plan	Pre-specified endpoints	Pre-specified analyses		

Orkin 2019: Low numbers of women (15.4%), Blacks/African Americans (18.5%), and those with high baseline viral loads (>100000 copies/mL, 21.3%), low CD4+ T-cell counts (≤200/mm3, 12.4%), or hepatitis B/C co-infections (2.7%).

6 DOL/LAM vs TDF/FTC/DOL

		1. Biases arising from the randomisation process			
Study name/ NCT number		**1.1 Was the allocation sequence random?**	**1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?**	**1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?**	**Risk of bias judgement**
NCT02831673 (GEMINI-1) and NCT02831764 (GEMINI-2)	Judgement	Yes	Yes	No	Low
	Description	Central randomisation schedule generated with SAS	Treatment assignment was done in accordance with a central randomisation schedule generated with SAS	Key demographic and baseline clinical characteristics were well balanced between the treatment groups	

		2. Bias due to deviations from the intended intervention (Effect of assignment to intervention)							
Study name/ NCT number		**2.1 Were participants aware of their assigned intervention during the trial?**	**2.2 Were carers and trial people delivering the interventions aware of the participants assigned intervention during the trial?**	**2.3 If yes/ probably yes/no information to 2.1 or 2.2, were there deviations from the intended intervention that arose because of the trial context?**	**2.4 If yes/ probably yes to 2.3, were these deviations likely to have affected the outcomes?**	**2.5 If yes/possibly yes/no information to 2.4 Were these deviations from intended intervention balanced between groups?**	**2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?**	**2.7 If no/ probably no/no information to 2.6. Was there potential for a substantial impact (on the result) of the failure to analyse the participants in the group to which they had been randomised?**	**Risk of bias judgement**
NCT02831673 (GEMINI-1) and NCT02831764 (GEMINI-2)	Judgement	No	No	NA	NA	NA	Yes	NA	Low
	Description	Double blind; the study masked both participants and	Double blind; the study masked both participants and	NA	NA	NA	Snapshot algorithm	NA	

		investigators to treatment assignment until week 96.	investigators to treatment assignment until week 96.						

		2. Risk of bias due to deviations from the intended interventions (Effect of adhering to intervention)						
Study name/ NCT number		**2.1 Were participants aware of their assigned intervention during the trial?**	**2.2 Were carers and people delivering the interventions aware of the participants assigned intervention during the trial?**	**2.3 [If applicable] If yes/probably yes/ no information to 2.1 or 2.2 Were important non-protocol interventions balanced across intervention groups?**	**2.4 [If applicable] Were there failures in implementing the intervention that could have affected the outcome?**	**2.5 [If applicable] Was there non-adherence to the assigned intervention regimen that could have affected participant's outcomes?**	**2.6. If no/probably no/no information to 2.3, or yes probably yes/no information to 2.4 or 2.5 Was an appropriate analysis used to estimate the effect of adhering to the intervention?**	**Risk of bias judgement**
NCT02831673 (GEMINI-1) and NCT02831764 (GEMINI-2)	Judgement	No	No	NA	NA	NA	NA	Low
	Description	Double blind; the study masked both participants and investigators to treatment assignment until week 96.	Double blind; the study masked both participants and investigators to treatment assignment until week 96.	NA	NA	NA	NA	

		3. Bias due to missing outcome data				
Study name/ NCT number		**3.1 Were outcome data available for all, or nearly all**	**3.2 If N/PN/NI to 3.1: Is there evidence that the result was**	**3.3 If N/PN/NI to 3.2: Could missingness in the outcome**	**3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the**	**Risk of bias judgement**

		participants randomised?	**not biased by missing outcome data?**	**depend on its true value?**	**outcome depended on its true value?**	
NCT02831673 (GEMINI-1) and NCT02831764 (GEMINI-2)	Judgement	Yes	NA	NA	NA	Low
	Description	5.3% missing data for virological outcomes at week 48 and 9.7% missing data for virological outcomes at week 96; similar between groups	NA	NA	NA	

		4. Bias in the measurement of the outcome					
Study name/ NCT number		**4.1 Was the method of measuring the outcome inappropriate?**	**4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?**	**4.3 If N/PN to 4.1 and 4.2: Were outcome assessors aware of the intervention received by the study participant?**	**4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?**	**4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?**	**Risk of bias judgement**
NCT02831673 (GEMINI-1) and NCT02831764 (GEMINI-2)	Judgement	No	No	No	NA	NA	Low
	Description	Snapshot algorithm	Snapshot algorithm	Double-blind	NA	NA	

		5. Risk of bias in selection of the reported result				**RCT overall risk of bias**
Study name/ NCT number		**5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that**	**5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from**	**5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from**	**Risk of bias judgement**	

		was finalized before unblinded outcome data were available for analysis?	**multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?**	**multiple eligible analyses of the data?**		
NCT02831673 (GEMINI-1) and NCT02831764 (GEMINI-2)	Judgement	Yes	No	No	Low	Low
	Description	Pre-specified analysis plan	Pre-specified endpoints	Pre-specified analyses		

Cahn 2019: Enrolled mostly men younger than 50 years; female participants were limited to those using contraceptives and who were not pregnant when initiating treatment. People with HIV-1 RNA of more than 500 000 copies per mL, hepatitis B virus infection or resistance mutations excluded.

7 DOL vs RALT + any 2 NRTIs

		1. Biases arising from the randomisation process			
Study name/ NCT number		**1.1 Was the allocation sequence random?**	**1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?**	**1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?**	**Risk of bias judgement**
NCT01227824; SPRING-2	Judgement	Yes	Yes	No	Low
	Description	Computer-generated	Central procedure using phone and web interface	Baseline demographics and disease characteristics were similar between treatment groups	

		2. Bias due to deviations from the intended intervention (Effect of assignment to intervention)							
Study name/ NCT number		**2.1 Were participants aware of their assigned intervention during the trial?**	**2.2 Were carers and trial people delivering the interventions aware of the participants assigned intervention during the trial?**	**2.3 If yes/ probably yes/no information to 2.1 or 2.2, were there deviations from the intended intervention that arose because of the trial context?**	**2.4 If yes/ probably yes to 2.3, were these deviations likely to have affected the outcomes?**	**2.5 If yes/possibly yes/no information to 2.4 Were these deviations from intended intervention balanced between groups?**	**2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?**	**2.7 If no/ probably no/no information to 2.6. Was there potential for a substantial impact (on the result) of the failure to analyse the participants in the group to which they had been randomised?**	**Risk of bias judgement**
NCT01227824; SPRING-2	Judgement	No	No	NA	NA	NA	Yes	NA	Low
	Description	Double-blind	Double-blind	NA	NA	NA	Intent-to-treat snapshot analysis	NA	

		2. Risk of bias due to deviations from the intended interventions (Effect of adhering to intervention)						
Study name/ NCT number		**2.1 Were participants aware of their assigned intervention during the trial?**	**2.2 Were carers and people delivering the interventions aware of the participants assigned intervention during the trial?**	**2.3 [If applicable] If yes/probably yes/ no information to 2.1 or 2.2 Were important non-protocol interventions balanced across intervention groups?**	**2.4 [If applicable] Were there failures in implementing the intervention that could have affected the outcome?**	**2.5 [If applicable] Was there non-adherence to the assigned intervention regimen that could have affected participant's outcomes?**	**2.6. If no/probably no/no information to 2.3, or yes probably yes/no information to 2.4 or 2.5 Was an appropriate analysis used to estimate the effect of adhering to the intervention?**	**Risk of bias judgement**
NCT01227824; SPRING-2	Judgement	No	No	NA	NA	NA	NA	Low
	Description	Double-blind	Double-blind	NA	NA	NA	NA	

		3. Bias due to missing outcome data				
Study name/ NCT number		**3.1 Were outcome data available for all, or nearly all participants randomised?**	**3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?**	**3.3 If N/PN/NI to 3.2: Could missingness in the outcome depend on its true value?**	**3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?**	**Risk of bias judgement**
NCT01227824; SPRING-2	Judgement	No	No	Yes	Yes	Low at week 48; high at week 96
	Description	7% missing data for virological outcomes in each group at week 48; 14% vs 13% at week 96.	The difference between week 48 and week 96 responses was driven mainly by discontinuations for reasons other than adverse events; the proportion of virological non-response was	The difference between week 48 and week 96 responses was driven mainly by discontinuations for reasons other than adverse events; the proportion of virological non-response was	The difference between week 48 and week 96 responses was driven mainly by discontinuations for reasons other than adverse events; the proportion of virological non-response was	

			unchanged for dolutegravir from week 48 to week 96, whereas it rose by 2% for raltegravir from week 48 to week 96	unchanged for dolutegravir from week 48 to week 96, whereas it rose by 2% for raltegravir from week 48 to week 96	unchanged for dolutegravir from week 48 to week 96, whereas it rose by 2% for raltegravir from week 48 to week 96	

		4. Bias in the measurement of the outcome					
Study name/ NCT number		**4.1 Was the method of measuring the outcome inappropriate?**	**4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?**	**4.3 If N/PN to 4.1 and 4.2: Were outcome assessors aware of the intervention received by the study participant?**	**4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?**	**4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?**	**Risk of bias judgement**
NCT01227824; SPRING-2	Judgement	No	No	No	NA	NA	Low
	Description	Snapshot algorithm	Snapshot algorithm	Double-blind	NA	NA	

		5. Risk of bias in selection of the reported result				**RCT overall risk of bias**
Study name/ NCT number		**5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?**	**5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within**	**5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?**	**Risk of bias judgement**	

			the outcome domain?			
NCT01227824; SPRING-2	Judgement	Yes	No	No	Low	Low at week 48; high at week 96 for virological outcomes
	Description	NCT record posted in October 2010 at start of recruitment	Pre-specified endpoints	Pre-specified analysis populations		

SPRING-2: A limitation of this study is the low number of non-white and female patients enrolled, which is not fully representative of the HIV global epidemic.

NRTI backbone comparison

8 TDF/FTC vs TAF/FTC with any 3rd agent

		1. Biases arising from the randomisation process			
Study name/ NCT number		**1.1 Was the allocation sequence random?**	**1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?**	**1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?**	**Risk of bias judgement**
NCT03122262; ADVANCE	Judgement	Yes	Yes	No	Low
	Description	Electronically generated	Electronically generated	Baseline characteristics were balanced across the groups	
NCT01780506 (also known as GS-US-292-0104) and NCT01797445 (also known as GS-US-292-0111)	Judgement	Yes	Yes	No	Low
	Description	Computer generated	Automated treatment assignment	Baseline characteristics were balanced across the groups	
NCT02431247; AMBER	Judgement	Yes	Yes	No	Low
	Description	Computer-generated interactive web-response system	Computer-generated interactive web-response system	Baseline characteristics were balanced between the two groups	
NCT01565850 (GS-US-299-0102)	Judgement	Yes	Yes	No	Low
	Description	Randomised centrally by a third party interactive voice/web response	Randomised centrally by a third party interactive voice/web response	Baseline demographic and general disease characteristics were similar between groups	

		2. Bias due to deviations from the intended intervention (Effect of assignment to intervention)							
Study name/ NCT number		**2.1 Were participants aware of their assigned intervention during the trial?**	**2.2 Were carers and trial people delivering the interventions aware of the participants assigned intervention**	**2.3 If yes/ probably yes/no information to 2.1 or 2.2, were there deviations from the intended**	**2.4 If yes/ probably yes to 2.3, were these deviations likely to have affected the outcomes?**	**2.5 If yes/possibly yes/no information to 2.4 Were these deviations from intended**	**2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?**	**2.7 If no/ probably no/no information to 2.6. Was there potential for a substantial impact (on the result) of the**	**Risk of bias judgement**

			during the trial?	**intervention that arose because of the trial context?**		**intervention balanced between groups?**		**failure to analyse the participants in the group to which they had been randomised?**	
NCT03122262; ADVANCE	Judgement	Yes	Yes	No information	NA	NA	Yes	NA	Some concerns
	Description	Open label	Open label	No details	NA	NA	Intention-to-treat analysis. After the testing for noninferiority, the treatment groups were compared for differences in efficacy. For these tests, an overall 1.7% significance level (P = 0.017) was used, to adjust for the three pairwise treatment comparisons being made.	NA	
NCT01780506 (also known as GS-US-292-0104) and NCT01797445 (also known as GS-US-292-0111)	Judgement	No	No	NA	NA	NA	Yes	NA	Low
	Description	Double-blind	Double-blind	NA	NA	NA	Intention to treat	NA	
NCT02431247; AMBER	Judgement	No	No	NA	NA	NA	Yes	NA	Low
	Description	Double-blind	Double-blind	NA	NA	NA	Intention to treat	NA	
	Judgement	No	No	NA	NA	NA	Yes	NA	Low

NCT01565850 (GS-US-299-0102)	Description	Double-blind	Double-blind	NA	NA	NA	Intention to treat	NA	

		2. Risk of bias due to deviations from the intended interventions (Effect of adhering to intervention)						
Study name/ NCT number		**2.1 Were participants aware of their assigned intervention during the trial?**	**2.2 Were carers and people delivering the interventions aware of the participants assigned intervention during the trial?**	**2.3 [If applicable] If yes/probably yes/ no information to 2.1 or 2.2 Were important non-protocol interventions balanced across intervention groups?**	**2.4 [If applicable] Were there failures in implementing the intervention that could have affected the outcome?**	**2.5 [If applicable] Was there non-adherence to the assigned intervention regimen that could have affected participant's outcomes?**	**2.6. If no/probably no/no information to 2.3, or yes probably yes/no information to 2.4 or 2.5 Was an appropriate analysis used to estimate the effect of adhering to the intervention?**	**Risk of bias judgement**
NCT03122262; ADVANCE	Judgement	Yes	Yes	No information	NA	NA	No information	Some concerns
	Description	Open label	Open label	No details	NA	NA	No details	
NCT01780506 (also known as GS-US-292-0104) and NCT01797445 (also known as GS-US-292-0111)	Judgement	No	No	NA	NA	NA	NA	Low
	Description	Double-blind	Double-blind	NA	NA	NA	NA	
NCT02431247; AMBER	Judgement	No	No	NA	NA	NA	NA	Low
	Description	Double-blind	Double-blind	NA	NA	NA	NA	
NCT01565850 (GS-US-299-0102)	Judgement	No	No	NA	NA	NA	NA	Low
	Description	Double-blind	Double-blind	NA	NA	NA	NA	

		3. Bias due to missing outcome data				
Study name/ NCT number		**3.1 Were outcome data available for all, or nearly all participants randomised?**	**3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?**	**3.3 If N/PN/NI to 3.2: Could missingness in the outcome depend on its true value?**	**3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?**	**Risk of bias judgement**
NCT03122262; ADVANCE	Judgement	No	No	Yes	Yes	High risk at week 48. Low at week 96
	Description	By week 48, the number of patients who had discontinued treatment or who had missing data was 41 (12%) in the TAF-based group, 39 (11%) in the TDF-based group, and 55 (16%) in the standard-care group. By week 98 the numbers of patients who had no virological data, including those who discontinued for any reason other than lack of efficacy and those with missing data within the visit window were: 64/351 (18.2%) in the TAF-based group, 62 (17.7%) in the TDF-based group, 126/702 (17.9%) in the combined DOL groups and 78/351 (22.2%) in the standard-care group (not significantly different).	Differences in efficacy between the groups at 48 weeks were driven by a higher number of discontinuations in the standard-care group than in the other two groups. In the per-protocol analysis, the percentage of patients with an HIV-1 RNA level <50 copies/mL was similar across the groups at week 48 (96% in the TAF-based group, 95% in the TDF-based group, and 96% in the standard-care group). At week 96, the difference in rate of missing data was similar between groups, and the differences in virological outcomes between groups were not significant either when missing data were classified as	Differences in efficacy between the groups were driven by the number of discontinuations	Differences in efficacy between the groups were driven by the number of discontinuations	

			treatment failures or when missing were excluded.			
NCT01780506 (also known as GS-US-292-0104) and NCT01797445 (also known as GS-US-292-0111)	Judgement	Yes	NA	NA	NA	Low
	Description	Data missing for 0.6% for virological outcomes	NA	NA	NA	
NCT02431247; AMBER	Judgement	Yes	NA	NA	NA	Low
	Description	Data missing for 6% for virological outcomes	NA	NA	NA	
NCT01565850 (GS-US-299-0102)	Judgement	No	No	Yes	Yes	High risk
	Description	Data missing for 6.5% for virological outcomes overall but not balanced between groups	The difference in virologic response rates at week 48 was primarily driven by the higher rate of participants in the TAF group (6.8%) compared with the TDF group (2%) who discontinued study drug with last available VL <50 copies/mL (e.g. due to reasons other than virologic failure such as loss to follow-up or investigator's discretion).	Differences in efficacy between the groups were driven by the number of discontinuations	Differences in efficacy between the groups were driven by the number of discontinuations	

		4. Bias in the measurement of the outcome					
Study name/ NCT number		**4.1 Was the method of measuring the**	**4.2 Could measurement or ascertainment of the outcome**	**4.3 If N/PN to 4.1 and 4.2: Were outcome assessors aware**	**4.4 If Y/PY/NI to 4.3: Could assessment of the outcome**	**4.5 If Y/PY/NI to 4.4: Is it likely that assessment of**	**Risk of bias judgement**

		outcome inappropriate?	**have differed between intervention groups?**	**of the intervention received by the study participant?**	**have been influenced by knowledge of intervention received?**	**the outcome was influenced by knowledge of intervention received?**	
NCT03122262; ADVANCE	Judgement	No	No	Yes	Probably no	NA	Low risk
	Description	The primary end point was the percentage of patients with an HIV-1 RNA level < 50 copies/mL at week 48. Secondary objectives were to evaluate additional viral-load thresholds, CD4 count changes, and side-effect profile and safety, including findings on physical examination, laboratory analyses, and dual-energy x-ray absorptiometry (DXA) scans.	Independent objective measurements as well as data from symptom screening, vital-signs measurement, symptom-directed physical examination, laboratory assessments, and multiple questionnaires, including a sleep questionnaire	Open label	Independent objective measurements as well as data from symptom screening, vital-signs measurement, symptom-directed physical examination, laboratory assessments, and multiple questionnaires, including a sleep questionnaire	NA	
NCT01780506 (also known as GS-US-292-0104) and NCT01797445 (also known as GS-US-292-0111)	Judgement	No	No	No	NA	NA	Low
	Description	Proportion of patients with plasma HIV-1 RNA less than 50 copies per mL at week 48 as defined by the US Food and Drug Administration (FDA) snapshot algorithm	Objective outcomes; double-blind	Double-blind	NA	NA	
	Judgement	No	No	No	NA	NA	Low

NCT02431247; AMBER	Description	Percentage viral load <50 copies/mL (FDA-snapshot analysis)	Objective outcomes; double-blind	Double-blind	NA	NA	
NCT01565850 (GS-US-299-0102)	Judgement	No	No	No	NA	NA	Low
	Description	Percentage viral load <50 copies/mL (FDA-snapshot analysis)	Objective outcomes; double-blind	Double-blind	NA	NA	

		5. Risk of bias in selection of the reported result				**RCT overall risk of bias**
Study name/ NCT number		**5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?**	**5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?**	**5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?**	**Risk of bias judgement**	
NCT03122262; ADVANCE	Judgement	Yes	No	No	Low	High risk at 48 weeks Some concerns at 96 weeks
	Description	Pre-specified analysis plan	Pre-specified endpoints	Pre-specified analyses		
NCT01780506 (also known as GS-US-292-0104) and NCT01797445 (also known as GS-US-292-0111)	Judgement	Yes	No	No	Low	Low
	Description	Pre-specified analysis plan	Pre-specified endpoints	Pre-specified analyses		
NCT02431247; AMBER	Judgement	Yes	No	No	Low	Low
	Description	Pre-specified analysis plan	Pre-specified endpoints	Pre-specified analyses		
	Judgement	Yes	No	No	Low	High risk

NCT01565850 (GS-US-299-0102)	Description	Pre-specified analysis plan	Pre-specified endpoints	Pre-specified analyses		

Advance: Strengths include generalisability, with representation from across the region and within South Africa, relatively few entry and exclusion criteria, the high proportion of women included, and the fact that participants were recruited from routine HIV testing and care programmes.

Amber: study limitations were inclusion of more than 80% white patients and a comparatively small proportion of female or older (>50 years) participants or who had high viral loads.

Mills: Relatively few women enrolled

Sax 2015: a small proportion of study participants with advanced HIV disease, a small proportion of women participants, and the exclusion of patients with chronic hepatitis B virus infection

ADVANCE had good generalisability but AMBER included >80% white patients and a comparatively small proportion of female or older (>50 years) participants or who had high viral loads; Mills 2015 enrolled relatively few women and Sax 2015 enrolled a small proportion of women or participants with advanced HIV disease, and excluded patients with chronic hepatitis B virus infection.

9 ABC/3TC vs TAF/FTC with any 3rd agent

		1. Biases arising from the randomisation process			
Study name/ NCT number		**1.1 Was the allocation sequence random?**	**1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?**	**1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?**	**Risk of bias judgement**
NCT02607930; GS-US-380-1489; 2015-004024-54 (EudraCT Number)	Judgement	Yes	Yes	No	Low
	Description	Computer-generated allocation sequence	Automated treatment assignment	Demographics and baseline characteristics were similar between groups	

		2. Bias due to deviations from the intended intervention (Effect of assignment to intervention)							
Study name/ NCT number		**2.1 Were participants aware of their assigned intervention during the trial?**	**2.2 Were carers and trial people delivering the interventions aware of the participants assigned intervention during the trial?**	**2.3 If yes/ probably yes/no information to 2.1 or 2.2, were there deviations from the intended intervention that arose because of the trial context?**	**2.4 If yes/ probably yes to 2.3, were these deviations likely to have affected the outcomes?**	**2.5 If yes/ possibly yes/no information to 2.4 Were these deviations from intended intervention balanced between groups?**	**2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?**	**2.7 If no/ probably no/no information to 2.6. Was there potential for a substantial impact (on the result) of the failure to analyse the participants in the group to which they had been randomised?**	**Risk of bias judgement**
NCT02607930; GS-US-380-1489; 2015-004024-54 (EudraCT Number)	Judgement	No	No	NA	NA	NA	Yes	NA	Low
	Description	Investigators, participants, and study staff giving treatment, assessing outcomes, and collecting data were masked to group assignment.	Investigators, participants, and study staff giving treatment, assessing outcomes, and collecting data were masked to group assignment.	NA	NA	NA	Full analysis set (all participants who were randomly assigned and had received at least one dose of the study drug, regardless of whether they returned for post-baseline assessments)	NA	

		2. Risk of bias due to deviations from the intended interventions (Effect of adhering to intervention)						
Study name/ NCT number		**2.1 Were participants aware of their assigned intervention**	**2.2 Were carers and people delivering the interventions aware of the**	**2.3 [If applicable] If yes/probably yes/ no information to**	**2.4 [If applicable] Were there failures in implementing**	**2.5 [If applicable] Was there non-adherence to the assigned**	**2.6. If no/probably no/no information to 2.3, or yes**	**Risk of bias judgement**

		during the trial?	**participants assigned intervention during the trial?**	**2.1 or 2.2 Were important non-protocol interventions balanced across intervention groups?**	**the intervention that could have affected the outcome?**	**intervention regimen that could have affected participant's outcomes?**	**probably yes/no information to 2.4 or 2.5 Was an appropriate analysis used to estimate the effect of adhering to the intervention?**	
NCT02607930; GS-US-380-1489; 2015-004024-54 (EudraCT Number)	Judgement	No	No	NA	NA	NA	NA	Low
	Description	Investigators, participants, and study staff giving treatment, assessing outcomes, and collecting data were masked to group assignment.	Investigators, participants, and study staff giving treatment, assessing outcomes, and collecting data were masked to group assignment.	NA	NA	NA	NA	

		3. Bias due to missing outcome data				
Study name/ NCT number		**3.1 Were outcome data available for all, or nearly all participants randomised?**	**3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?**	**3.3 If N/PN/NI to 3.2: Could missingness in the outcome depend on its true value?**	**3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?**	**Risk of bias judgement**
NCT02607930; GS-US-380-1489; 2015-004024-54 (EudraCT Number)	Judgement	Yes	NA	NA	NA	Low
	Description	<6% missing values for virological outcomes at 48 weeks and <10% missing values for virological outcomes at 96 weeks	NA	NA	NA	

		4. Bias in the measurement of the outcome

Study name/ NCT number		**4.1 Was the method of measuring the outcome inappropriate?**	**4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?**	**4.3 If N/PN to 4.1 and 4.2: Were outcome assessors aware of the intervention received by the study participant?**	**4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?**	**4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?**	**Risk of bias judgement**
NCT02607930; GS-US-380-1489; 2015-004024-54 (EudraCT Number)	Judgement	No	No	No	NA	NA	Low
	Description	Snapshot algorithm	Snapshot algorithm	Investigators, participants, and study staff giving treatment, assessing outcomes, and collecting data were masked to group assignment.	NA	NA	

		5. Risk of bias in selection of the reported result				**RCT overall risk of bias**
Study name/ NCT number		**5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?**	**5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?**	**5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?**	**Risk of bias judgement**	
NCT02607930; GS-US-380-1489; 2015-004024-54 (EudraCT Number)	Judgement	Yes	No	No	Low	Low
	Description	Pre-specified analysis plan	Pre-specified endpoints	Pre-specified analyses		