Appendix 3: GRADE tables

3.1 What to Start: Which NRTI backbone:

Design: RCTs, Systematic reviews

Population: ART naive
Intervention: which NRTI backbone (TDF/FTC or ABC/3TC)
Outcomes: Viral load, CD4 count, HIV resistance, adverse events, clinical events

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

OUTCOME	IMPORTANCE
Viral suppression (<50) at week 48	9: critical
Viral suppression at week 96	8: critical
Proportion of all randomised subjects with protocol-defined virological failure at week 48 +/- week 96	9: critical
Proportion of all randomised subjects who develop drug resistance	8: critical
Quality of life	8: critical
Proportion discontinuing for adverse events	7: critical
Proportion with grade 3/4 adverse events (overall)	7: critical
Proportion with grade 3/4 rash	7: critical
Proportion with grade 3/4 ALT/AST elevation	7: critical
Proportion with grade 3/4 CNS events	5: important
Proportion with grade 3/4 diarrhoea	5: important
10% or more limb fat loss	5: important
% change in limb fat	5: important
% change in trunk fat	5: important
% change in visceral adipose tissue	5: important
Change in visceral:total adipose tissue ratio	5: important
Renal impairment	4: important
Proportion with grade 3/4 total cholesterol events	3: not important
Proportion with grade 3/4 LDL cholesterol	3: not important

Proportion with grade 3/4 triglycerides	3: not important
Total hip BMD decrease 6% or more	3: not important
Total spine BMD decrease 6% or more	3: not important
Change in lumbar spine BMD	3: not important
Change in hip BMD	3: not important
Bone fractures	3: not important

Three randomised trials were found comparing these two NRTI backbones:

- ACTG5202:
  - Sax *et al.* Abacavir–Lamivudine versus Tenofovir–Emtricitabine for Initial HIV-1 Therapy. New Engl J Med 2009; 361(23): 2230-40 (ClinicalTrials.gov number, NCT00118898).
  - Sax *et al.* Abacavir/ Lamivudine Versus Tenofovir DF/Emtricitabine as Part of Combination Regimens for Initial Treatment of HIV: Final Results. J Infect Dis 2011; 204: 1191–201.
  - Daar ES et al. Atazanavir Plus Ritonavir or Efavirenz as Part of a 3-Drug Regimen for Initial Treatment of HIV-1 A Randomized Trial. *Ann Intern Med.* 2011; 154: 445-456.
  - McComsey GA *et al*. Bone Mineral Density and Fractures in Antiretroviral-Naive Persons Randomized to Receive Abacavir-Lamivudine or Tenofovir Disoproxil Fumarate-Emtricitabine Along With Efavirenz or Atazanavir-Ritonavir: AIDS Clinical Trials Group A5224s, a Substudy of ACTG A5202. J Infect Dis 2011; 203: 1791-801.
  - McComsey GA *et al*. Peripheral and Central Fat Changes in Subjects Randomized to Abacavir-Lamivudine or Tenofovir-Emtricitabine With Atazanavir-Ritonavir or Efavirenz: ACTG Study A5224s. Clinical Infectious Diseases 2011; 53(2): 185–196.

- ASSERT
  - Post *et al*. Randomized Comparison of Renal Effects, Efficacy, and Safety With Once-Daily Abacavir/ Lamivudine Versus Tenofovir/ Emtricitabine, Administered With Efavirenz, in Antiretroviral-Naive, HIV-1–Infected Adults: 48-Week Results From the ASSERT Study. J Acquir Immune Defic Syndr 2010; 55(1): 49-57.
  - Stellbrink HJ et al. Comparison of Changes in Bone Density and Turnover with Abacavir-Lamivudine versus Tenofovir-Emtricitabine in HIV-Infected Adults: 48-Week Results from the ASSERT Study. Clin Infect Dis 2010; 51: 963-72.
  - Moyle, G. J., H. J. Stellbrink, et al. (2010). "Comparison of bone and renal toxicities in the ASSERT study: Final 96 week results from a prospective randomized safety trial." Antiviral Therapy 15: A19.

- HEAT
  - Smith *et al.* Randomized, double-blind, placebo-matched, multicenter trial of abacavir/ lamivudine or tenofovir/ emtricitabine with lopinavir/ ritonavir for initial HIV treatment. AIDS 2009; 23(12): 1547-56.

Also, one meta-analysis was identified. This reviewed 12 trials (3399 subjects on TDF/FTC, 1769 ABC/3TC, with a boosted PI [Hill A, Sawyer W. Effects of nucleoside reverse transcriptase inhibitor backbone on the efficacy of first-line boosted highly active antiretroviral therapy based on protease inhibitors: metaregression analysis of 12 clinical trials in 5168 patients. HIV Med 2009;10(9):527-35]). It included prospective clinical trials of HAART regimens containing RTV-boosted HIV PIs in antiretroviral-naïve, HIV-infected individuals published between 1 January 2000 and 1 March 2008; trials had to involve at least 50 chronically infected treatment-naïve, HIV-infected individuals aged 16 years or above at any stage of HIV infection; the minimum duration of follow-up reported for these trials at the moment of inclusion in the systematic review had to be 48 weeks; efficacy data had to be reported for the 48-week timepoint using the FDA-endorsed TLOVR algorithm for the virological response (% of patients with a plasma viral load <50 copies/mL); they had to evaluate, in at least one treatment arm, HAART regimens comprising an RTV-boosted PI (a PI co-administered with ≤200 mg/day of RTV) and a fixed combination of two NRTIs: either ABC or TDF in combination with 3TC or FTC. The included studies were not all head-to-head comparisons of TDF vs ABC – the only included study that was a head-to-head trial was HEAT (included above). The authors stated that "The interpretation of all results should be made with the caveat that there was a wide range of baseline patient characteristics and all trials not were conducted identically. While statistical models to account for baseline variables and the usage of the ITT TLOVR endpoint may help to reduce the impact of any baseline imbalance, this is not guaranteed." They also state that "There may be other differences between the trials – in country selection, adherence, patient management – that could explain the difference in efficacy between the NRTIs, but could not be adjusted for in the multivariate analysis." There is likely to be so much heterogeneity between trial methodologies that combining them in this way is difficult. In addition, the authors have combined means and medians, which may not be valid if the underlying population distributions are skewed. The information from this analysis could not be used further.

Evidence tables

Reference	**Study type and methodological quality**	**No. pts**	**Patient characteristics**	**Intervention**	**Comparison**	**Length follow-up**	**Outcome measures**	**Funding**
ACTG5202: **Sax** *et al.* Abacavir–Lamivudine versus Tenofovir–Emtricitabine for Initial HIV-1 Therapy. New Engl J Med **2009**;	**RCT** **Allocation to treatment** Random Method of randomisation: Allocation used a	**Total N: 1858** **First analysis includes data from the 797 patients**	**INCLUSION CRITERIA** HIV-1–infected patients who were at least 16 years of age, who had received at most 7 days of antiretroviral	**Drug(s):** 300mg tenofovir DF plus 200mg emtricitabine	**Drug(s):** 600mg abacavir plus 300 mg lamivudine (plus 600mg	**Treatment duration:** planned and actual study	**Primary endpoint:** time from randomization to virologic failure (defined as a confirmed HIV-1 RNA level > or = 1000 copies/ ml at or after	Abbott Pharmaceuticals, Bristol-Myers Squibb,

361(23): 2230-40 (ClinicalTrials.gov number NCT00118898). **Sax** *et al.* Abacavir/ Lamivudine Versus Tenofovir DF/ Emtricitabine as Part of Combination Regimens for Initial Treatment of HIV: Final Results. J Infect Dis **2011**; 204: 1191–201. **Daar** ES et al. Atazanavir Plus Ritonavir or Efavirenz as Part of a 3-Drug Regimen for Initial Treatment of HIV-1 A Randomized Trial. Ann Intern Med **2011**; 154: 445-456. **McComsey** GA et al. **Bone** Mineral Density and Fractures in	centralized computer system. Randomization was stratified according to the screening HIV-1 RNA level obtained before study entry (≥ 100,000 vs. <100,000 copies per milliliter), with the use of a permuted-block design with dynamic balancing according to the main institution Concealment: adequate **Blinding** double blinded with regard to NRTIs **Sample size calculation** Regimens were considered equivalent if the two-sided 95% confidence interval for the hazard ratio was between 0.71 and 1.40. A planned sample size of 1800 subjects (450 per group) would provide an 89.8% probability of declaring	**with a screening HIV-1 RNA level of 100,000 copies per milliliter or more.** 718 patients (90%) remained in the study. Follow-up was discontinued in 41 patients assigned to abacavir–lamivudine and in 38 patients assigned to tenofovir DF–emtricitabine, with no significant difference in the distributions of time to	therapy previously, and who had acceptable laboratory values. **EXCLUSION CRITERIA** pregnant or breastfeeding; were using immunomodulators; had any known allergies to the study drugs; abused substances that would interfere with the study; had a serious illness; had an important cardiac conduction disorder; required prohibited medications; showed evidence of major resistance mutations; were incarcerated; or, as of July 2006, had hepatitis B. Resistance testing was required for recently infected patients. **Baseline**	(Truvada) (plus 600mg efavirenz or 300mg atazanavir plus 100mg ritonavir) **n=399 in first sub-group analysis (HIV-1 RNA levels of 100 000 copies/mL or more at screening)** **n=530 in second sub-group analysis**	efavirenz or 300mg atazanavir plus 100mg ritonavir) **n=398 in first sub-group analysis (HIV-1 RNA levels of 100 000 copies/mL or more at screening)** **n=530 in second sub-group analysis (HIV-1 RNA levels < 100 000 copies/mL at screening**	duration 96 weeks after enrolment of last patient **Assessments at:** before entry, at entry, at weeks 4, 8, 16, and 24, and every 12 weeks thereafter **Follow-up after end of treatment:** none **Median follow-up first analysis**	16 weeks and before 24 weeks, or ≥ 200 copies /ml at or after 24 weeks) Other endpoints: Time from the initiation of treatment to the first grade 3 or 4 sign, symptom, or laboratory abnormality that was at least one grade higher than that at baseline, excluding isolated unconjugated hyper-bilirubinemia and elevations in the creatine kinase level, while the patient was receiving the randomly assigned treatment. Adverse events Coprimary objectives of A5224s were to compare effects of starting ABC-3TC with those of TDF/FTC on spine and hip BMD and on body fat. A5224s 2ry objectives	Gilead Sciences, and GlaxoSmithKline provided the study medications and had input into the protocol development and review of the manuscript.

Antiretroviral-Naive Persons Randomized to Receive Abacavir-Lamivudine or Tenofovir Disoproxil Fumarate-Emtricitabine Along With Efavirenz or Atazanavir-Ritonavir: AIDS Clinical Trials Group A5224s, a Substudy of ACTG A5202. J Infect Dis **2011**; 203: 1791-801. **McComsey** GA et al. Peripheral and Central **Fat** Changes in Subjects Randomized to Abacavir Lamivudine or Tenofovir-Emtricitabine With Atazanavir-Ritonavir or Efavirenz: ACTG Study A5224s. Clinical Infectious	equivalence if two regimens were the same, assuming uniform accrual, exponential virologic failure, and lost-to-follow-up time distributions among the four groups, with event probabilities of 17.46% and 10.00%, respectively, at 48 weeks. Study conduct and safety data were reviewed yearly by the data and safety monitoring board. Efficacy data were reviewed annually starting with the second review of study data. Early stopping guidelines for inferiority were prespecified, with a regimen considered to be inferior if the 99.95% two-sided confidence interval for the hazard ratio for virologic failure did not include 1.0. **ITT analysis**	discontinuation (P = 0.91). **Second analysis: low screening HIV RNA stratum (n=1060)**	**comparability between groups**: yes **Age**: median 38 years (IQR 31-45) **Gender**: 83% male **Severity of disease:** median CD4 cell count 229.5cells/ml (IQR 89.5-333.8) Specific A5224s exclusion criteria were uncontrolled thyroid disease or hypogonadism; endocrine diseases, including Cushing's syndrome, diabetes mellitus, and the use of growth hormone, anabolic steroids, glucocorticoids, or osteoporosis medications; or the intent to start bone-related treatment.	**(HIV-1 RNA levels < 100 000 copies/ mL at screening)** A5224s was a substudy of AIDS Clinical Trials Group (ACTG) A5202: for n in each group see results section	**)** A5224s was a substudy of AIDS Clinical Trials Group (ACTG) A5202: for n in each group see results section	**:** 60 weeks (range 0-112 weeks); **full analysis :** 136 weeks Median (25th, 75th percentile) **final** (Daar 2011) follow-up was **138 weeks** (106 weeks, 169 weeks)	were to compare BMD changes between EFV and ATV/r arms, to compare TDF-FTC with ABC-3TC and EFV with ATV/r on BMD changes at week 48, and to compare % with bone fractures. Substudy evaluations included whole-body dual-energy X-ray absorptiometry (DEXA) scans at baseline and weeks 24, 48, 96, 144, and 192 and a single-slice abdomen CT scan at the L4-L5 level at baseline and week 96. Fat distribution was measured by DEXA in antero-posterior view (with use of Hologic or Lunar scanners). Technicians were instructed to use the same machine on the same subject throughout the study. CT was used to	

Diseases **2011**; 53(2): 185–196.	Yes **Setting:** Outpatients						quantify visceral adipose tissue (VAT) and total adipose tissue (TAT).	

Patient disposition (data from both Sax publications)

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

*VF=virological failure

Combining high and low strata: TDF/FTC

All (n=1857)			
TDF/FTC (n=929)		ABC/3TC (n=928)	
with EFV (n=464)	with ATV (n=465)	with EFV (n=465)	with ATV (n=463)
VF: 44/464	44/465	64/465	67/463
88/929		131/928	

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

sex, race or ethnic group, age, HIV-1 RNA level, CD4 cell count, and available or unavailable test results for HIV-1 genotype at screening.

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

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

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

Other outcomes:

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

High HIV RNA stratum	tenofovir DF–emtricitabine (n=399)	abacavir–lamivudine (n=398)	hazard ratio, CI, p value
at least one grade 3 or 4 sign, symptom, or laboratory abnormality that was at least one grade higher than the baseline value, while receiving their initial regimen	78	130	
grade 4 event	13	24	
time to the safety end point			1.89; 95% CI, 1.43 to 2.50; P<0.001
week 48 median change in total cholesterol level	26mg/dl	34mg/dl	P<0.001
week 48 median change in HDL cholesterol level	7mg/dl	9mg/dl	P=0.05

week 48 median change in triglyceride level	3mg/dl	25mg/dl	P = 0.001
median change in total: HDL cholesterol ratio	−0.2	−0.2	P = 0.50
Suspected study drug–related hypersensitivity	27 (7%)	27 (7%); 1 died	
Subsequent virologic failure among patients with suspected drug hypersensitivity	3	4	
AIDS events	17 (4%)	26 (7%)	
HIV-related cancers	4	8	
Bone fractures	10	7	
Myocardial infarctions	0	0	
Renal failure	2	2	
median change from baseline in creatinine clearance	2ml/min (IQR −11 to 16); n=241	4ml/min(IQR −7 to 16); n=212	P = 0.10

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

Main (final results) publication:

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

low HIV RNA stratum: virologic failure (with EFV)	33/265 (12%)	39/266 (15%)	HR 1.23 (95% CI, 0.77, 1.96)	

CD41 Cell Count Changes in the Low HIV RNA Stratum

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

Tolerability Endpoints in the Low HIV RNA Stratum

Low HIV RNA stratum	tenofovir DF–emtricitabine (n=530)	abacavir–lamivudine (n=530)	hazard ratio, CI, p value
time to first antiretroviral drug modification			ATV/r: HR 1.43 (95% CI, 1.06, 1.92, P = .018); EFV: HR 1.48 (95% CI, 1.12, 1.95, P = .005).
time to first modification of the NRTIs			ATV/r: HR 1.57 (95% CI 1.14, 2.16, P = .006); ETV: HR 1.84 (95% CI 1.36, 2.51, P < .0001)
unblinding of NRTIs for suspected drug hypersensitivity ATV/r EFV severe hypersensitivity reaction when rechallenged	 11 (4 renal) 8 (5 renal) 1	 23 32 0	
Safety event Time to first safety event with ATV/r Time to first safety event with EFV			 HR 1.13; 95% CI 0.83 to 1.54 P=.44 HR 1.38; 95% CI, 1.03, 1.85, P = .03
Death with ATV with EFV	 0 3 (bacterial pneumonia, stroke, Mycobacterium	 4 (non-Hodgkin's lymphoma, MI, car accident, drug overdose/ suicide) 3 (bladder carcinoma, hepatic	

	avium complex)	carcinoma, unknown)	
Cardiovascular events with ATV/r with EFV	34 15/265 (6%) 19/265 (7%)	29 15/264 (6%) 14/266 (5%)	
Bone fractures with ATV/r with EFV	 10/265 (4%) 13/265 (5%)	 7/264 (3%) 15/266 (6%)	
Site-reported incidence of renal disease with ATV/r with EFV	 7/265 (3%) 5/265 (2%)	 10/264 (4%) 10/266 (4%)	

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

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

	ABC (n = 263)	TDF (n = 265)	ABC (n = 264)	TDF (n = 263)	All subjects (n = 1055) who started medication
	ATV/r		EFV		
Overall, n (%)	80 (30)	98 (37)	78 (29)	83 (32)	339 (32)
Metabolic, n (%)	22 (8)	19 (7)	24 (9)	13 (5)	78 (7)
Total cholesterol (fasting), n	4	1	9	4	

LDL (fasting), n	7	7	15	8	
Triglycerides (fasting), n	8	3	5	0	
Glucose (nonfasting)	2	5	0	1	
Gastrointestinal, n (%)	21 (8)	16 (6)	12 (5)	12 (5)	61 (6)
Diarrhoea/loose stool, n.	2	4	8	2	
ALT, n	7	1	1	6	
Nausea and/or vomiting, n	6	3	3	1	
Neuropsychological, n (%)	8 (3)	1 (<1)	16 (6)	14 (5)	39 (4)
Depression, n.	3	0	3	7	
General body, n (%)	29 (11)	30 (11)	42 (16)	30 (11)	131 (12)
Ache/pain/discomfort, n	20	11	12	17	
Fever, n	6	7	6	1	
Asthenia/fatigue, n	3	3	7	3	
Rash/allergic reaction, n	2	2	5	2	
Headache, n	3	3	6	1	
Hematologic, n (%)	1 (<1)	7 (3)	4 (2)	7 (3)	19 (2)
Neutrophil count, n	1	6	4	7	

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

Daar 2011 Publication:

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

Variable	Abacavir–Lamivudine		Tenofovir DF–Emtricitabine	
	Efavirenz	Atazanavir Ritonavir	Efavirenz	Atazanavir Ritonavir

Time to virologic failure				
Baseline Persons at risk, n	465	463	464	465
96 wk Events/persons at risk (Kaplan–Meier estimate), n/n (%)	63/331 (14.7)	72/338 (16.6)	44/367 (10.2)	48/364 (11.0)
Difference in 96-wk Kaplan–Meier estimate (95% CI), %	1.9 (2.9 to 6.8)		0.8 (3.3 to 4.9)	
Full follow-up Events/total person-years at risk, n/n	72/1011.7	83/1017.1	57/1095.6	57/1086.4
Estimated HR (95% CI)	1.13 (0.82 to 1.56) NB no difference by viral load stratum (p=0.147)		1.01 (0.70 to 1.46) NB no difference by viral load stratum (p=0.37)	
Time to primary safety end point (1st grade-3 or -4 sign, symptom, or lab abnormality while receiving originally assigned 3rd drug (atazanavir/ritonavir or efavirenz) that was ≥1 grade higher than baseline, excluding isolated unconjugated hyperbilirubinemia and creatine kinase)				
Baseline persons at risk, n	461	462	461	464
96 wk Events/persons at risk (Kaplan–Meier estimate), n/n (%)	175/176 (41.7)	152/229 (35.5)	126/248 (30.2)	119/268 (27.7)
Difference in 96-wk Kaplan–Meier estimate (95% CI), percentage points; P value	6.2 (12.9 to 0.4); 0.066		2.5 (8.6 to 3.7); 0.43	
Full follow-up Events/total person-years at risk, n/n	187/631.2	170/762.5	147/814.3	141/868.9
Estimated HR (95% CI); P value	0.81 (0.66 to 1.00); 0.048 no difference in effect by viral load stratum (*P*=0.71)		0.91 (0.72 to 1.15); 0.44 no difference in effect by viral load stratum (*P*=0.85)	
Time to AIDS or death	HR, 0.93 [CI, 0.56 to 1.54]; *P* = 0.77		HR, 1.23 [CI, 0.70 to 2.39]; *P* =0.42	
Time to primary tolerability end point (1st change in therapy, ignoring NRTIs)				
Baseline Persons at risk, n	461	462	461	464
96 wk Events/persons at risk (Kaplan–Meier estimate), n/n (%)	155/290 (33.7)	110/334 (23.9)	114/328 (24.8)	97/347 (21.0)
Difference in 96-wk Kaplan–Meier estimate (95% CI),	9.8 (15.6 to 4.0); 0.001		3.8 (9.2 to 1.6); 0.170	

percentage points; P value				
Full follow-up Events/total person-years at risk, n/n	186/943.7	142/1052.6	142/1032.1	126/1088.5
Estimated HR (95% CI); P value	0.69 (0.56 to 0.86); <0.001 no difference by viral load stratum (*P* = 0.63)		0.84 (0.66 to 1.07); 0.166 no difference by viral load stratum (*P* = 0.90).	

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

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

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

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

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

Safety events

	Abacavir–Lamivudine		**Tenofovir DF–emtricitabine**	
	Efavirenz (n = 461)	**Atazanavir/ Ritonavir (n = 462)**	**Efavirenz (n = 461)**	**Atazanavir/ Ritonavir (n = 464)**
Death, n (of the 1857 randomly assigned patients)	11	8	6	6
Selected primary safety end point event, n (%): overall	187 (41)	170 (37)	147 (32)	141 (30)
Fasting total cholesterol level	21	11	7	2
Fasting LDL cholesterol level	29	14	15	7
Fasting triglycerides level	17	16	5	7
Blood glucose level	4	7	2	4
Gastrointestinal	23 (5)	38 (8)	22 (5)	25 (5)
AST	6	14	6	6
ALT	5	13	9	5
Diarrhoea or loose stools	11	7	6	6
Nausea, vomiting, or both	5	8	2	3
Neuropsychological	28 (6)	14 (3)	28 (6)	10 (2)
Depression	6	4	13	5
Dizzy or lightheaded	6	0	2	2
Insomnia, dreams, or sleep	6	0	5	0
General	71 (15)	64 (14)	46 (10)	59 (13)
Ache, pain, or discomfort	25	35	23	21
Fever	10	16	4	12

Asthenia, fatigue, or malaise	8	5	7	8
Headache	10	7	3	6
Rash or allergic rash	9	3	4	6
Vascular events (coronary artery disease, infarction, ischemia, angina, CVA, TIA or peripheral vascular disease)	2 (<1%)	2 (<1%)	6 (1%)	1 (<1%)
Renal diagnoses of the Fanconi syndrome, toxic nephropathy, proteinuria, or renal failure	5 (1%)	4 (1%)	3 (1%)	6 (1%)
bone fractures	22 (5%)	16 (3%)	21 (5%)	21 (5%)
suspected hypersensitivity reaction	53 (11%)	34 (7%)	25 (5%)	27 (6%)

Of the 269 pts with protocol-defined virologic failure, 265 had resistance data available at failure and baseline; of these, 25 had major mutations at baseline. Among pts with virologic failure, emergent resistance mutations were less frequent in those assigned to received atazanavir plus ritonavir than in those assigned to receive efavirenz, combined with either NRTI ($P < 0.001$ for both). There was also a lower frequency of NRTI-associated mutations among pts on ATZ/r than on efavirenz with abacavir–lamivudine ($P < 0.001$) or tenofovir DF–emtricitabine ($P = 0.046$).

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

*Excludes patients with major resistance mutations present at baseline but includes 1 person who had resistance data available at virologic failure but

not at baseline. Total may not add up to 100% because some patients had >1 mutation. Values are total number (% of pts randomly assigned) [% of pts with a genotype and without baseline resistance]

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

	Efavirenz + TDF (n =69)	**Efavirenz + ABC (n = 70)**	**ATZ/R + TDF (n = 65)**	**ATZ/R + ABC (n = 65)**
Median age (IQR)	40 (33-44)	39 (31-46)	38 (30-44)	37 (29-43)
Male	58 (84%)	56 (80%)	56 (86%)	59 (91%)
Median (IQR) CD4 cells/µL	250 (132-334)	213 (106-350)	247 (114-319)	222 (75-332)
Median (IQR) lumbar spine BMD (g/cm^2)	1.12 (1.00-1.23)	1.08 (.97-1.23)	1.13 (1.03-1.24)	1.13 (1.04-1.23)
Median (IQR) hip BMD (g/cm^2)	0.99 (.92-1.07)	1.02 (.93-1.11)	1.05 (.98-1.18)	1.02 (.97-1.13)
Mean (SD) change lumbar spine BMD (%), week 0-96	-2.52 (4.08), n=54, p<0.001	-.78 (5.20), n=53, p=0.28	-4.38 (4.95), n=43, p<0.001	-1.99 (4.69), n=48, p=0.005
Mean (SD) change in hip BMD (%), week 0-96	-3.69 (3.81), n=54, p<0.001	-2.54 (4.40), n=51, p<0.001	-4.31 (5.17), n=42, p<0.001	-2.68 (3.30), n=48, p<0.001

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

Changes by NRTI Components: Primary Analysis.

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

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

Changes by NNRTI-PI Component: Secondary Analysis.

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

Changes by NRTI Components: Primary Analysis.

At week 96, ITT analysis showed that the ABC-3TC arms had a significantly smaller decrease in mean % change in hip BMD, compared with the TDF-FTC

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

Changes by NNRTI-PI Component: Secondary Analysis.

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

The ITT analyses of mean % change from entry to week 96 of spine and hip BMD were adjusted for the following prespecified baseline covariates that could affect BMD, first individually and then jointly, with use of linear regression: NNRTI-PI (or NRTI components for the NNRTI-PI analyses), spine BMD (or hip BMD for corresponding analysis), sex, age, race/ethnicity, $\log_{10}$ HIV-1 RNA load, CD4 cell count, and BMI. For analyses of the NRTI component effect or the NNRTI-PI component effect, all of the adjusted models led to results similar to those of the unadjusted analyses. In the 96-week % change in lumbar spine BMD, multivariable analysis, ABC-3TC (vs TDF-FTC) p=0.003 and ATV/r (vs EFV) p=0.039 were significant and in the 96-week % change in hip BMD, multivariable analysis, ABC-3TC (vs TDF-FTC) was significant p=0.033.

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

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

McComsey lipodystrophy paper

Variable	EFV/ TDF-FTC (n = 56)	EFV /ABC-3TC (n = 53)	ATV-r/ TDF-FTC (n = 45)	ATV-r / ABC-3TC (n = 49)
No. pts with ≥ 10% limb fat loss	8	10	7	8
Prevalence of ≥ 10% limb fat loss	14.3 (6.4–26.2)	18.9 (9.4–32.0)	15.6 (6.5–29.5)	16.3 (7.3–29.7)

(primary analysis), % (95% CI)				
No. pts with ≥ 20% limb fat loss	5	2	0	3
Prevalence of ≥ 20% limb fat loss (post hoc analysis), % (95% CI)	8.9 (3.0–19.6)	3.8 (0.5–13.0)	0.0 (0.0–7.9)	6.1 (1.3–16.9)
Mean (SD) change in limb fat (%) wk 0–96	15.3 (36.7) n=56, p=0.003	17.7 (30.7) n=53, p<0.001	27.8 (36.4) n=45, p<0.001	32.7 (48.0) n=49, p<0.001
Mean (SD) change in trunk fat (%) wk 0–96	20.1 (44.1) n=56, p=0.001	22.2 (44.6) n=53, p=0.001	35.9 (50.7) n=45, p<0.001	37.0 (58.3) n=49, p<0.001
Mean (SD) change in VAT (%) wk 0–96	14.8 (48.7) n=54, p=0.03	9.9 (45.1) n=51, p=0.12	29.5 (88.4) n=45, p=0.031	23.7 (41.4) n=45, p<0.001
Mean (SD) change in VAT:TAT ratio (%) wk 0–96	-0.2 (19.7) n=54, p=0.95	-1.9 (20.9) n=51, p=0.52	-2.2 (19.1) n=45, p=0.44	-2.3 (21.4) n=45, p=0.48

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

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

	combining ABC-3TC and TDF-FTC, within the **ATV-r** arms	combining ABC-3TC and TDF-FTC, within the **EFV** arms	difference, p value
mean absolute and percentage changes in limb fat	1.88 kg and 30.4%	0.96 kg and 16.5%	difference (Δ) 0.93 kg (95% CI, 0.24–1.61; P = .008) and 13.9% (95% CI, 3.3%–24.5%; P = .010)
mean absolute and percentage changes in trunk fat	2.42 kg; 36.5%	1.33 kg; 21.1 %	Δ= 1.09 kg (95% CI, 0.15–2.03; P = .023) and 15.4% (95% CI, 1.7%–29.0%; P = .028).
absolute and percentage changes from baseline in VAT and VAT:TAT ratio			Δ= 7.6 cm^2 (95% CI, -2.4 to 17.7; P = .14), 14.2% (95% CI, -2.2% to 30.6%; P = .090) and 0.00 (95% CI, -0.02 to 0.02; P = .92).
gains in mean BMI (post hoc endpoint)			Δ=0.88 kg/m^2; 95% CI, 0.13–1.62; P 5 .022

Authors' conclusion

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

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

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

Reference	Study type/ methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Length follow-up	Outcome measures	Funding
ASSERT Post *et al*. Randomized Comparison of Renal Effects, Efficacy, and Safety With Once-Daily Abacavir/ Lamivudine Versus Tenofovir/ Emtricitabine, Administered With Efavirenz, in Antiretroviral-Naive, HIV-1–Infected Adults: 48-Week Results From the ASSERT Study. J Acquir Immune Defic Syndr 2010; 55(1): 49-57. Stellbrink HJ et al. Comparison of Changes in Bone Density and Turnover with Abacavir-Lamivudine versus Tenofovir-	**RCT** **Allocation to treatment** Random Method of randomisation: unclear Concealment: unclear **Blinding** not blinded **Sample size calculation** stated **ITT analysis** Yes **Setting:** Outpatients	**Total N:** 392 randomised; 385 received treatment. At the week 48 data cut-off, 107 subjects (28%) had withdrawn prematurely, 63 subjects (33%) receiving abacavir/ lamivudine, and 44 subjects (23%) receiving tenofovir/ emtricitabine.	**INCLUSION CRITERIA** HIV; antiretroviral-naive (no previous therapy with any nonnucleoside reverse transcriptase inhibitor and ≤14 days of prior therapy with any other antiretroviral), HLA-B*5701-negative adults (≥18 years of age) with a plasma HIV-1 RNA ≥1000 copies per milliliter at screening. **EXCLUSION CRITERIA** estimated creatinine clearance <50 mL per minute (Cockcroft-Gault method) during the screening period; subjects with an active, AIDS-defining illness at baseline; subjects positive for hepatitis B; subjects were assessed for transmitted resistance to the antiretrovirals in the study using the Virco TYPE HIV-1 assay:	**n=197 randomised; 193 exposed** **Drug(s):** tenofovir/emtricitabine	**n=195 randomised; 192 exposed** **Drug(s):** abacavir/ lamivudine	**Treatment duration:** 96 weeks **Assessments at:** week 4, week 12, and thereafter every 12 weeks. **Follow-up after end of treatment:** 2–4 weeks after the completion of treatment for any subject with an ongoing adverse	**Primary endpoint:** change from baseline in eGFR (MDRD), at week 48 Other endpoints: change from baseline in eGFR (Cockcroft-Gault), proportion of subjects with decline from baseline in eGFR, and proportion of subjects with National Kidney Foundation chronic kidney disease, adverse events. Week 24 and 48 proportion of subjects with HIV-1 RNA <50 copies/mL, proportion of subjects with HIV-1 RNA <400 copies/mL, absolute values and change	GlaxoSmithKline

Emtricitabine in HIV-Infected Adults: 48-Week Results from the ASSERT Study. Clin Infect Dis 2010; 51: 963-72. Moyle, G. J., H. J. Stellbrink, et al. (2010). "Comparison of bone and renal toxicities in the ASSERT study: Final 96 week results from a prospective randomized safety trial." Antiviral Therapy 15: A19.			subjects with evidence of resistance at screening or prior documented evidence of genotypic and/or phenotypic resistance were excluded. **Baseline comparability between groups**: yes **Age**: median 37.0 (range 18–70) years **Gender**: 81% male **Severity of disease:** median CD4 cell count 240 (range 10–610) cells/ml			event	from baseline in HIV-1 RNA and CD4+ cell count, CD4+ and CD8+ lymphocyte counts, and HIV-1–associated conditions. Virologic failure (defined as failure to achieve a 1-log reduction in HIV-1 RNA by wk 4, or a confirmed rebound to ≥400 copies/mL after confirmed reduction to <400 copies/mL by wk 24, or confirmed HIV-1 RNA ≥400 copies/mL after wk 24.	

Main outcomes:

At week 48, the adjusted mean change from baseline in eGFR by MDRD was +0.22 mL/min/1.73 m^2 and +1.18 mL/min/1.73 m^2 for the abacavir/lamivudine and tenofovir/emtricitabine arms, respectively. The adjusted mean difference between arms was 0.953 mL/min/1.73 m^2 [95% confidence interval (CI): -1.445 to +3.351, P = 0.435]. No differences were observed between treatment arms in the proportion of subjects with a decline from baseline in eGFR of ≥10 mL/min, >20 mL/min, 10%, or 20% when estimated by either MDRD or Cockcroft-Gault or the proportion of subjects with renal failure using the National Kidney Foundation chronic kidney disease stage categories.

Other outcomes:

	tenofovir/emtricitabine	abacavir/lamivudine	difference between groups
Prematurely withdrawn Withdrawn for adverse events	44/193 (23%) 20/193 (10%)	63/192 (33%) 25/192 (13%)	
At week 48 achieved HIV-1 RNA <400 copies/mL	148 of 193 (77%)	129 of 192 (67%)	difference 9.5%, 95% CI: 0.6 to 18.4*

At week 48 achieved HIV-1 RNA <50 copies/mL low viral load subgroup (<100,000 copies/mL) high viral load subgroup (≥100,000 copies/mL)	137 of 193 (71%) 75% (62 of 83) 68% (75 of 110)	114 of 192 (59%) 64% (61 of 95) 55% (53 of 97)	difference 11.6%, 95% CI: 2.2 to 21.1*
Protocol-defined virologic failures at week 48	2	6	
Median CD4+ cell count increases at week 48	+150 cells/mm3; n = 156	+150 cells/mm3; n = 136	
HIV-1 disease progression to Centers for Disease Control and Prevention Class C or death.	5/193 (3%)	3/192 (2%)	

* Difference between treatment arms driven by investigator reported lack of efficacy and early withdrawals (occurring before virologic suppression), specifically from AEs. Administrative discontinuations (e.g. lost to follow-up, protocol violation, subject decision) in the study were unusually high and higher in the abacavir/lamivudine arm. Despite HLA B*5701 testing, differences in the rate of withdrawals due to AEs between the arms was driven by drug hypersensitivity events.

Three pts (all on abacavir/lamivudine) developed efavirenz-associated mutations (K103N, V106M, and G190A/G) and 1 of these also developed K65R, D67N mutations. 3 wks before the wk 36 virologic failure time point, this pt started the prohibited medication St Johns Wort (contraindicated with efavirenz); it potentially decreases efavirenz levels, leading to increased viral load and possible resistance to efavirenz or cross-resistance to other anti-HIV drugs.

	tenofovir/emtricitabine	abacavir/lamivudine
withdrawals due to AEs	<1%	6%
drug-related (investigator opinion) AEs drug-related grade 2–4 AEs (dizziness, abnormal dreams, and drug hypersensitivity were the most common AEs and occurred in both arms)	91/193 (47%) 20%	98/192 (51%) 29%
Drug hypersensitivity, including abacavir HSR clinically suspected abacavir HSRs (no reports of abacavir rechallenge/death)	1/193 (<1%) -	12/192 (6%) 6 (3%)
cardiac AE by week 48	4/193 (2%) included 1 MI	5/192 (3%) included 1 intracardiac thrombus: this subject had suffered an MI before participating in the trial
increases from baseline in median TC	0.66 mg/dL	1.36 mg/dL
increases from baseline in median triglycerides	0.05 mg/dL	0.23 mg/dL
increases from baseline in median low-density lipoprotein cholesterol	0.39 mg/dL	0.81 mg/dL
increases from baseline in median HDL-cholesterol	0.28 mg/dL	0.38 mg/dL
reduction in mean TC/HDL cholesterol ratio	-0.934	-0.599

Authors' conclusion
No differences in eGFR were observed between the arms, although increases in markers of tubular dysfunction were observed in the tenofovir/emtricitabine arm. The long-term clinical significance of these results are unclear, and ASSERT continues through to 96 weeks to study this further.

Stellbrink 2010:

	TDF-FTC (*n* = 193)		ABC-3TC (*n* = 192)	
Variable	No. pts	No. (%) pts with ↓in BMD ≥6%	No. pts	No. (%) pts with ↓in BMD ≥6%
Total hip, actual relative time				
Week 24	160	6 (4%)	137	1 (<1%)
Week 48	143	18 (13%)	120	3 (3%)
Lumbar spine, actual relative time				
Week 24	165	17 (10%)	142	10 (7%)
Week 48	143	15 (10%)	126	6 (5%)

The adjusted mean % change from baseline in total hip BMD was -1.9% in the abacavir-lamivudine group and -3.6% in the tenofovir-emtricitabine group (treatment difference -1.7% (95% CI, -2.26 to -1.10; p<0.001. The adjusted mean % change from baseline in lumbar spine BMD was -1.6% in the abacavir-lamivudine group and -2.4% in the tenofovir-emtricitabine group (treatment difference, -0.8%; 95% CI, -1.61% to -0.06%; *P*=.036).

For those with Z score measurements at wk 48, both arms showed a small decrease in mean (+/-standard deviation [SD]) Z-score from baseline: -0.11+/-0.16 and -0.11+/-0.26 in the abacavir-lamivudine group for total hip and lumbar spine, respectively, and -0.24+/-0.18 and -0.22+/-0.33 in the tenofovir-emtricitabine group for total hip and lumbar spine, respectively.

Moyle abstract describes an analysis that explores changes in bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DXA) and bone turnover using biomarkers over 96 weeks. Changes in renal function were also examined.

Over 96 wks there was a continued ↓from baseline in hip BMD, and the difference between the arms remained significant (ABC/3TC -2.2%, TDF/FTC -3.5%; P<0.001). The BMD at the spine decreased initially and then increased between weeks 24 and 96 with the difference between the arms remaining significant to wk 48 but not to wk 96 (ABC/3TC -0.9%, TDF/FTC -1.7%; P=0.112). Bone turnover markers increased from baseline in both treatment arms over the first 24–48 weeks and subsequently decreased or stabilised. At week 96 there were significantly greater bone biomarker increases in the TDF/FTC arm compared with the ABC/3TC arm. No significant difference in change of eGFR from baseline was observed between the

arms (ABC/3TC +1.48ml/ min/1.73m2, TDF/FTC -1.15ml/min/1.73m2; P=0.06). Changes in glomerular function markers did not differ between arms.

Despite a high subject discontinuation rate (37% in ABC/3TC versus 33% in TDF/FTC), the overall virological failure rate was low for both treatment arms; a lower proportion of subjects achieved HIV RNA<50 copies/ml in the ABC/3TC arm (51%) compared with the TDF/FTC arm (59%). The adverse event rate was similar between arms with no new safety signal identified.

Reference	Study type/ methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
HEAT Smith *et al.* Randomized, double-blind, placebo-matched, multicenter trial of abacavir/ lamivudine or tenofovir/ emtricitabine with lopinavir/ ritonavir for initial HIV treatment. AIDS 2009; 23(12):	**RCT** **Allocation to treatment** Random Method of randomisation: unclear Concealment: unclear **Blinding** double blind **Sample size calculation** stated **ITT analysis** Yes **Setting:** Outpatients	**Total N:** 694 randomised and 688 received treatment; 66% (455/688) completed 96 weeks of study	**INCLUSION CRITERIA** ART-naive, HIV-1-infected patients, at least 18 years old with plasma HIV-1 RNA≥1000 copies/ml (c/ml) and any CD4+ cell count. **EXCLUSION CRITERIA** medical conditions compromising patient safety, use of prohibited medications, protocol-specified abnormal laboratory values, and estimated Cockcroft–Gault creatinine clearance below 50 ml/min. **Baseline comparability between groups**: yes **Age**: median 38 years	**n=345** **Drug(s):** TDF/FTC (300 mg/ 200 mg, Truvada) with open-label LPV/r (800mg/ 200mg, Kaletra)	**n=343** **Drug(s):** ABC/ 3TC (600 mg/ 300mg, Epzicom or Kivexa) with open-label LPV/r (800mg/ 200mg, Kaletra)	**Treatment duration:** 96 wks **Assessments at:** screening, baseline (day 1), and at wks 2, 6, 12, 18, 24, 32, 40, 48, 60, 72, 84, and 96, or withdrawal **Follow-up after end of treatment:** none	**Primary endpoint:** proportion of pts with HIV-1 RNA <50 c/ml at 48 wks (missing = failure, M=F) and the primary safety endpoint was the incidence of adverse events over 96 wks. Secondary endpoints: proportion with HIV-1 RNA < 400 c/ml, change in HIV-1 RNA and CD4+ cell counts, time to virologic failure, time to loss of virologic response (TLOVR), development of genotypic and phenotypic resistance at virologic failure, rate of blinded NRTI discontinuation due to suspected ABC HSR or PRTD, fasting lipid measures. Virologic failure was defined as either failure to achieve HIV-1RNA below 200 c/ml or confirmed	GlaxoSmithKline

1547-56.			**Gender**: 82% male **Severity of disease:** median CD4+ cell count was 202 cells/ml.				rebound to ≥200 c/ml after reduction to below 50 c/ml by wk 24. After wk 24, virologic failure was defined as a confirmed HIV-1 RNA rebound to ≥200 c/ml.	

Main outcomes:
Summary HIV RNA < 50 copies/ml at week 48

	tenofovir/emtricitabine	abacavir/lamivudine	95% CI for treatment difference
achieved an HIV-1 RNA < 50 c/ml at wk 48 wk 96	231/345 (67%) 200/345 (58%)	232/343 (68%) 205/343 (60%)	-6.63 to +7.40 (non-inferiority)
TLOVR	61%	63%	
MD is equal to F	62%	64%	
observed analyses of the ITT-E population	87%	84%	
patients with baseline HIV-1 RNA ≥100 000 c/ml: HIV-1 RNA < 50 c/ml at week 48 maintained this endpoint at week 96	 65% 58%	 63% 56%	
patients with baseline HIV-1 RNA < 100,000 c/ml < 50 c/ml at week 48 and at week 96.	 69% 58%	 71% 63%	
protocol-defined virologic failure	48 (14%)	49 (14%)	

Other outcomes:
At week 96, median CD4+ cell count increased by 250 cells/ml from baseline in the ABC/3TC group [IQR 148–358] and by 247 cells/ ml in the TDF/FTC group (IQR 149–359). Median CD4+ cell counts at week 96 in the ABC/3TC and TDF/ FTC groups were 466 and 445 cells/ml, respectively.

Drug-associated resistance as defined by the IAS-USA resistance guidelines was assessed for the 97 pts (14%) with protocol-defined virologic failure (ABC/3TC, 49; TDF/FTC, 48). 86 of these pts had paired baseline and on-treatment samples for genotypic and phenotypic analysis; 40/86 (47%) pts had virus with treatment-emergent mutations. 28/86 (33%) pts had virus with acquired NRTI associated mutations (ABC/3TC, 11; TDF/FTC, 17); the most common substitution occurred at codon 184 (ABC/3TC, 11; TDF/FTC, 17). 18/86 (21%) pts acquired minor protease inhibitor-associated mutations (ABC/3TC, 11; TDF/FTC, 7). One pt receiving ABC/3TC acquired primary protease inhibitor resistance. This pt had a documented re-exposure to HIV from a partner who was heavily ART experienced, prior to the virologic failure timepoint. Phenotypic results confirmed these genotypic findings.

	tenofovir/emtricitabine (n=345)	abacavir/lamivudine (n=343)
The proportion of grade 2–4 adverse events over 96 weeks	80%	80%
drug related grade 2–4 adverse events over 96 weeks	157 (46%)	171 (50%)
drug-related grade 2–4 diarrhoea	19%	19%
drug-related grade 2–4 nausea	6%	8%
drug-related grade 2–4 increased triglycerides	6%	6%
drug-related grade 2–4 increased cholesterol	4%	7%
drug-related grade 2–4 decreased GFR	5%	5%
grade 3–4 adverse events through week 96	97/345 (28%)	103/343 (30%)
considered drug related	52/345 (15%)	50/343 (15%)
grade 3-4 drug-related diarrhoea	1%	2%
grade 3-4 drug-related nausea	<1%	0%
grade 3-4 drug-related increased triglycerides	10 (3%)	7 (2%)
grade 3-4 drug-related increased cholesterol	3 (1%)	3 (1%)
grade 3-4 drug-related decreased GFR	2%	2%
SAEs (exclusive of ABC HSR) through 96 weeks	41/345 (12%)	31/343 (9%)
Drug-related SAEs	10 (3%)	18/343 (5%)
suspected ABC HSR	3 (<1%)	14 (4%)
Immune reconstitution syndrome	0	2 (<1%)
Anemia	1 (<1%)	1 (<1%)
Renal failure	2 (<1%)	0
Hepatoxicity	0	1 (<1%) Pt also had hep B
Sepsis	1 (<1%)	0
Decreased creatinine renal clearance	1 (<1%)	0
Pulmonary embolism	2 (<1%); 1 also had DVT	1 (<1%)
Changed LPV/r dosing from once daily to bd due to gastrointestinal intolerability	51 (15%)	59 (17%)
Study withdrawals due to an adverse event	22 (6%)	19 (6%)
suspected ABC HSR	0	2 (<1%)
renal failure	2 (<1%)	0
diarrhoea	2 (<1%)	1 (<1%)

vomiting nausea hyperlipidemia increased triglycerides increased aspartate aminotransferase mycobacterium–avium complex infection	2 (<1%) 2 (<1%) 1 (<1%) 2 (<1%) 1 (<1%) 2 (<1%)	1 (<1%) 0 2 (<1%) 3 (<1%) 2 (<1%) 0
Suspected ABC HSR grade 3 grade 4	3 (<1%) 1 0	14 (4%) 4 0
Drug-related death Death	0 7 (pneumonia, GI haemorrhage, cardiopulmonary failure after larynx surgery, disseminated mycobacterium infection, exacerbation of COPD and respiratory failure, progressive multifocal leukoencephalopathy, and AIDS in a patient with heavy ethanol use and depression)	0 1 (head trauma following a fall)
Progression to a more advanced CKD stage	49/328 (15%)	31/324 (10%)
progressed to stage 3 CKD (eGFR <60 ml/min/ 1.73m2)	11	4
progressed to stage 4 CKD (eGFR <30 ml/min/1.73m2)	0	0
proximal renal tubule dysfunction (PRTD; defined as a confirmed rise in serum creatinine of at least 0.5 mg/dl from baseline and serum phosphate below 2 mg/dl or either of the above accompanied by any two of the following: proteinuria (≥100 mg/dl), glycosuria (≥250 g/dl), low serum potassium (<3 mEq/l), or low serum bicarbonate (<19 mEq/l).	5 (1%): 4 men (two whites, one African–American, and one Other race) and 1 Japanese female patient; 2 pts had confounding risk factors at baseline; one was receiving trimethoprim–sulfamethoxazole concurrently and one was coinfected with hepatitis C. 2 switched to another nucleoside backbone, 4 recovered from the event, but recovery status was unknown for one who discontinued study prematurely	0
Grade 3/4 ALT elevations patients without coinfection with hepatitis B or C patients coinfected with hepatitis B, C, or both	4/339 2/306 2/33	8/340 3/295 5/45
Cardiovascular event	4 (cardiac arrest following a cocaine overdose, severe aggravated heart failure with congestive heart failure precipitated by worsening renal insufficiency, CVA in	2 (chest pain in a pt with history of angina and hypertension and

considered related to study drug	a patient with history of smoking, and TIA in a patient with history of hypertension and hypertriglyceridemia) 0	TIA in another pt with a history of hypertension and hypertriglyercidemia) 0

Median (range) laboratory parameters at baseline and 96 weeks

	ABC				TDF			
Median (mg/dl)	No. tested (baseline, wk 96)	Baseline	Week 96	Median change	No. tested (baseline, wk 96)	Baseline	Week 96	Median change
Total cholesterol: HDL ratio	278, 204	4.41 (1.70–40)	4.07 (1.72–18.25)	-0.27	286, 187	4.45 (1.81–89)	4 (2.04–12.13)	-0.44
Total cholesterol	279, 205	158 (71–264)	202 (106–334)	36	286, 188	159 (59–297)	186 (97–297)	28
HDL-cholesterol	278, 204	36 (3–80)	47 (8–137)	10	286, 189	35 (2–93)	47 (8–96)	12
LDL-cholesterol	261, 186	93 (4–197)	107 (10–222)	9	270, 172	92 (0–221)	94 (42–201)	8
Triglycerides	279, 205	122 (34–1153)	187 (54–1209)	54	286, 188	134 (40–968)	180 (53–1191)	42
Non-HDL-cholesterol	278, 204	123 (37–227)	150 (63–297)	25	286, 188	123 (39–239)	140 (71–258)	18
Glucose	343, 236	90 (46–286)	90 (28–383)	-1	344, 219	89 (61–576)	89 (47–266)	1
Insulin (mIU/ml)	323, 228	10 (1–158)	8 (1–438)	-1	330, 213	10 (1–95)	7 (1–204)	-2
MDRD GFR (ml/min/1.73)	339, 325	88 (36–208)	93 (36–180)	0	340, 333	87 (44–177)	88 (30–176)	0
C–G GFR (ml/min)	339, 325	103 (35–281)	112 (46–292)	7	340, 333	100 (45–211)	103 (35–282)	4

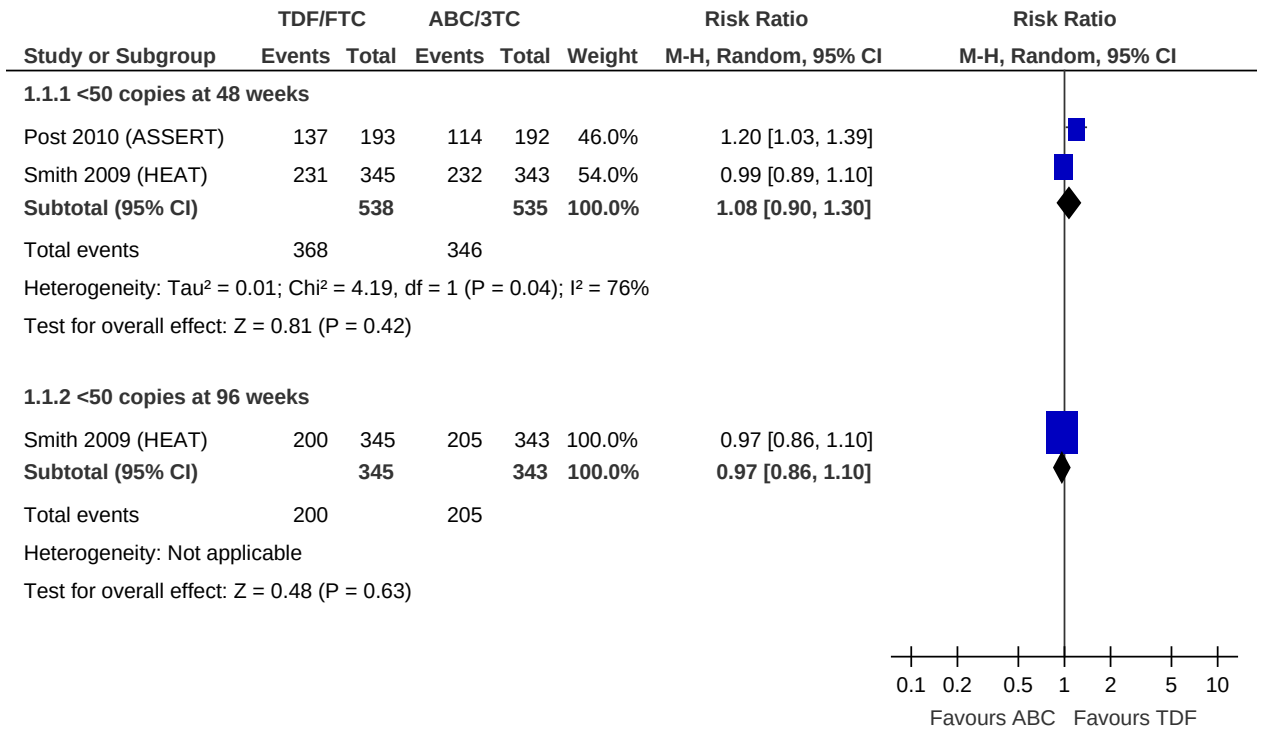
Authors' conclusion

ABC/3TCandTDF/FTC, each in combination with LPV/r, are highly effective initial regimens regardless of baseline viral load or CD4+ cell count. Long-

term virologic, immunologic, safety, tolerability, and antiretroviral resistance for ABC/3TC were similar to those with TDF/FTC over 96 wks. In this study, both ABC/3TC and TDF/FTC proved to be effective and well tolerated backbones for initial ART.

Forest plots

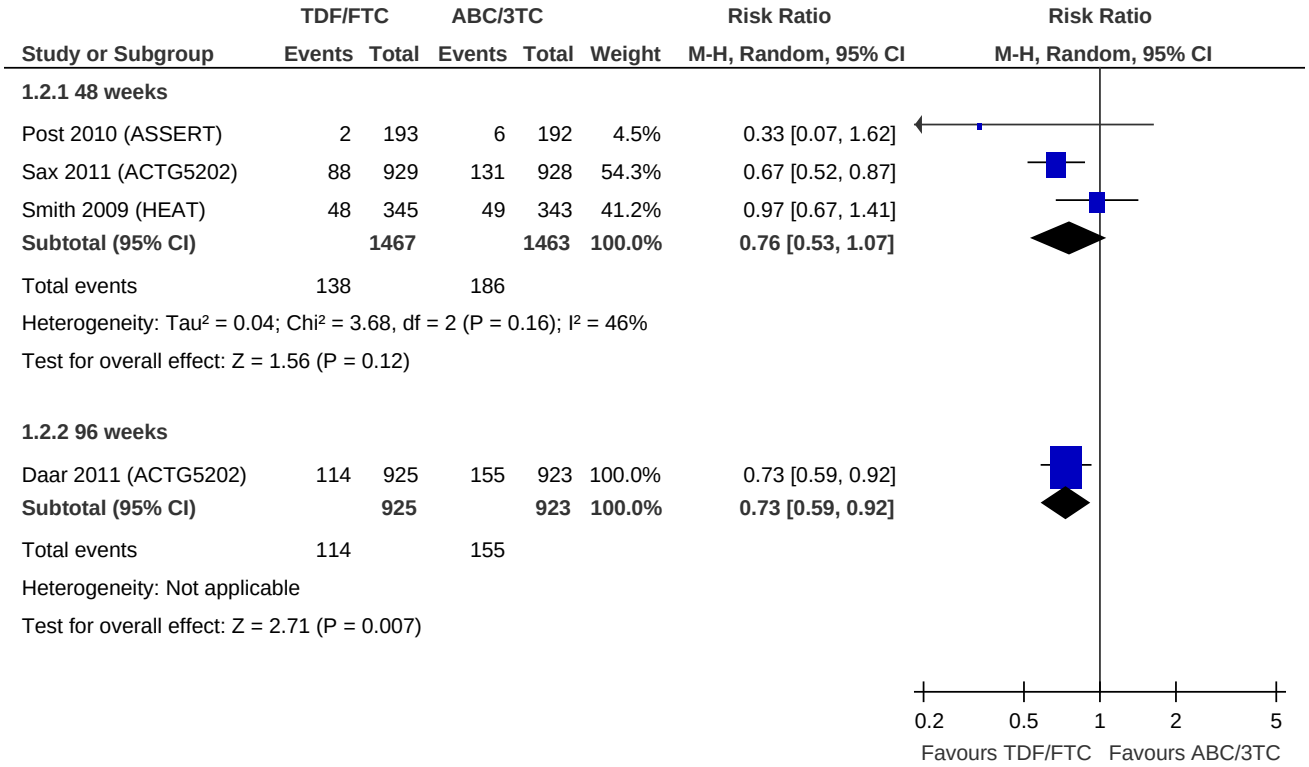
Viral suppression (<50) at week 48/week 96



No clear evidence of a difference between the treatment arms.

NB The authors of the ASSERT trial state that the difference between the treatment arms was driven by investigator reported lack of efficacy and early withdrawals (occurring before virologic suppression), specifically from AEs. Therefore the virological failure outcome (assuming comparable definitions between trials, see below) is probably a fairer comparison than the suppression outcome.

Proportion of all randomised subjects with protocol-defined virological failure at week 48 +/- week 96



There is statistical heterogeneity between these studies (I^2 = 46%) and also clinical heterogeneity in terms of the outcome definitions:

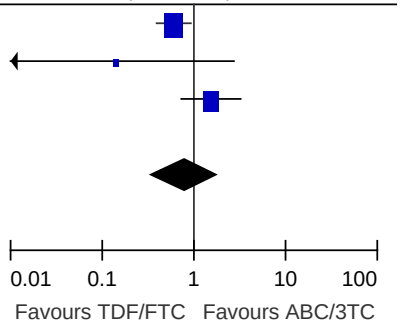
- In the ASSERT trial, virologic failure was defined in the protocol as failure to achieve a 1-log reduction in HIV-1 RNA by wk 4, or a confirmed rebound to ≥400 copies/mL after confirmed reduction to <400 copies/mL by wk 24, or confirmed HIV-1 RNA ≥400 copies/mL after wk 24.
- In the ACTG 5202 trial, the primary efficacy endpoint was HIV RNA levels > 1000 copies/mL at wks 16–24, or HIV RNA > 200 copies/mL after wk 24.
- In the HEAT trial, virologic failure was defined as either failure to achieve HIV-1RNA < 200 c/ml or confirmed rebound to ≥200 c/ml after reduction to below 50 c/ml by wk 24; after wk 24, virologic failure was defined as a confirmed HIV-1 RNA rebound to ≥200 c/ml.

Proportion of all randomised subjects who develop drug resistance

	TDF/FTC		ABC/3TC			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Daar 2011 (ACTG5202)	32	925	53	923	51.3%	0.60 [0.39, 0.93]	
Post 2010 (ASSERT)	0	193	3	192	7.6%	0.14 [0.01, 2.73]	
Smith 2009 (HEAT)	17	345	11	343	41.1%	1.54 [0.73, 3.23]	
Total (95% CI)		**1463**		**1458**	**100.0%**	**0.79 [0.33, 1.90]**	
Total events	49		67				

Heterogeneity: $Tau^2 = 0.34$; $Chi^2 = 5.79$, df = 2 (P = 0.06); $I^2 = 65\%$

Test for overall effect: Z = 0.52 (P = 0.60)



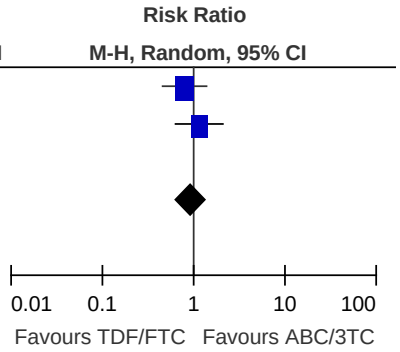
NB heterogeneity

Proportion discontinuing for adverse events

Study or Subgroup	TDF/FTC Events	TDF/FTC Total	ABC/3TC Events	ABC/3TC Total	Weight	Risk Ratio M-H, Random, 95% CI
Post 2010 (ASSERT)	20	193	25	192	53.7%	0.80 [0.46, 1.38]
Smith 2009 (HEAT)	22	345	19	343	46.3%	1.15 [0.63, 2.09]
Total (95% CI)		**538**		**535**	**100.0%**	**0.94 [0.63, 1.42]**
Total events	42		44			

Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 1 (P = 0.37); I² = 0%

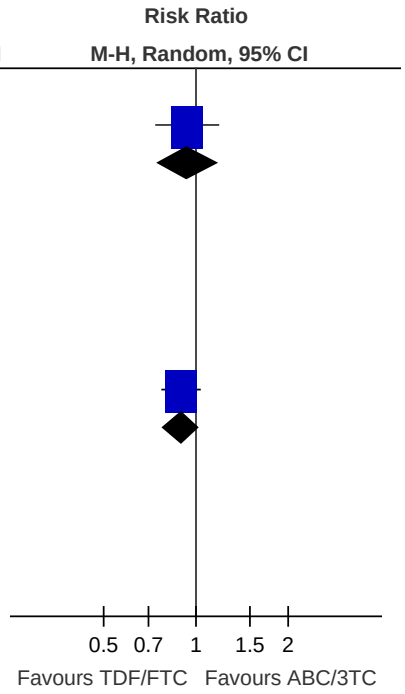
Test for overall effect: Z = 0.28 (P = 0.78)



No clear evidence of a difference between the treatment arms.

Proportion with any grade 3/4 adverse events

Study or Subgroup	TDF/FTC Events	TDF/FTC Total	ABC/3TC Events	ABC/3TC Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 96 weeks						
Smith 2009 (HEAT)	97	345	103	343	100.0%	0.94 [0.74, 1.18]
Subtotal (95% CI)		**345**		**343**	**100.0%**	**0.94 [0.74, 1.18]**
Total events	97		103			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.58)						
1.5.2 At end of follow up						
Daar 2011 (ACTG5202)	257	923	288	925	100.0%	0.89 [0.78, 1.03]
Subtotal (95% CI)		**923**		**925**	**100.0%**	**0.89 [0.78, 1.03]**
Total events	257		288			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						



No clear evidence of a difference between the treatment arms.

Proportion with grade 3/4 clinical events; proportion with grade 3/4 laboratory events; quality of life

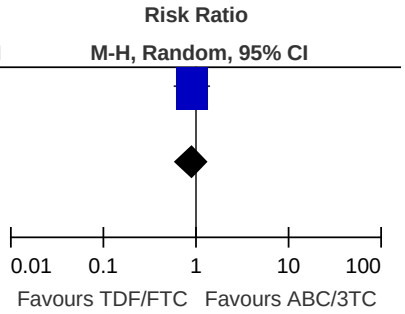
No data from these studies to address these outcomes.

Proportion with grade 3/4 neurological events

Study or Subgroup	TDF/FTC Events	TDF/FTC Total	ABC/3TC Events	ABC/3TC Total	Weight	Risk Ratio M-H, Random, 95% CI
Daar 2011 (ACTG5202)	38	925	42	923	100.0%	0.90 [0.59, 1.39]
Total (95% CI)		**925**		**923**	**100.0%**	**0.90 [0.59, 1.39]**
Total events	38		42			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.47 (P = 0.64)



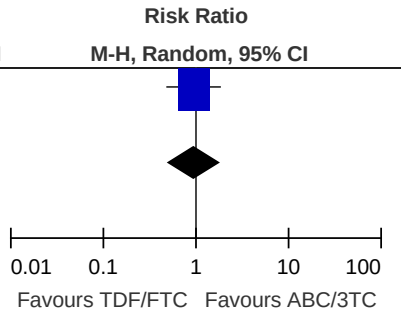
No clear evidence of a difference between the treatment arms.

Proportion with grade 3/4 diarrhoea

Study or Subgroup	TDF/FTC Events	TDF/FTC Total	ABC/3TC Events	ABC/3TC Total	Weight	Risk Ratio M-H, Random, 95% CI
Daar 2011 (ACTG5202)	17	925	18	923	100.0%	0.94 [0.49, 1.82]
Total (95% CI)		**925**		**923**	**100.0%**	**0.94 [0.49, 1.82]**
Total events	17		18			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.18 (P = 0.86)



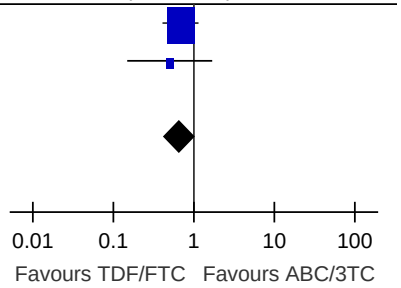
No clear evidence of a difference between the treatment arms.

Proportion with grade 3/4 ALT/AST elevation

Study or Subgroup	TDF/FTC Events	TDF/FTC Total	ABC/3TC Events	ABC/3TC Total	Weight	Risk Ratio M-H, Random, 95% CI
Daar 2011 (ACTG5202)	26	925	38	923	85.5%	0.68 [0.42, 1.11]
Smith 2009 (HEAT)	4	339	8	340	14.5%	0.50 [0.15, 1.65]
Total (95% CI)		**1264**		**1263**	**100.0%**	**0.65 [0.41, 1.03]**
Total events	30		46			

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

Test for overall effect: Z = 1.84 (P = 0.07)



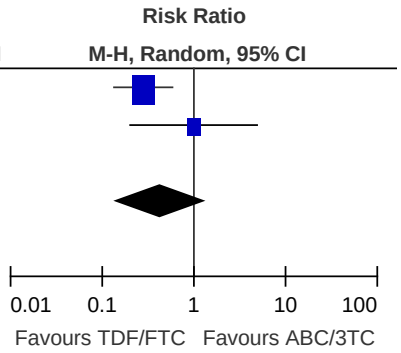
No clear evidence of a difference between the treatment arms.

Proportion with grade 3/4 total cholesterol

Study or Subgroup	TDF/FTC Events	TDF/FTC Total	ABC/3TC Events	ABC/3TC Total	Weight	Risk Ratio M-H, Random, 95% CI
Daar 2011 (ACTG5202)	9	925	32	923	66.2%	0.28 [0.13, 0.58]
Smith 2009 (HEAT)	3	345	3	343	33.8%	0.99 [0.20, 4.89]
Total (95% CI)		**1270**		**1266**	**100.0%**	**0.43 [0.13, 1.39]**
Total events	12		35			

Heterogeneity: Tau² = 0.40; Chi² = 2.00, df = 1 (P = 0.16); I² = 50%

Test for overall effect: Z = 1.41 (P = 0.16)



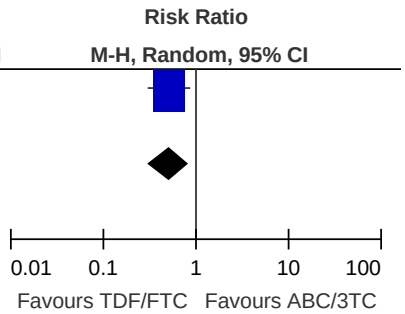
No clear evidence of a difference between the treatment arms.

Proportion with grade 3/4 LDL cholesterol

Study or Subgroup	TDF/FTC Events	TDF/FTC Total	ABC/3TC Events	ABC/3TC Total	Weight	Risk Ratio M-H, Random, 95% CI
Daar 2011 (ACTG5202)	22	925	43	923	100.0%	0.51 [0.31, 0.85]
Total (95% CI)		**925**		**923**	**100.0%**	**0.51 [0.31, 0.85]**
Total events	22		43			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.61 (P = 0.009)



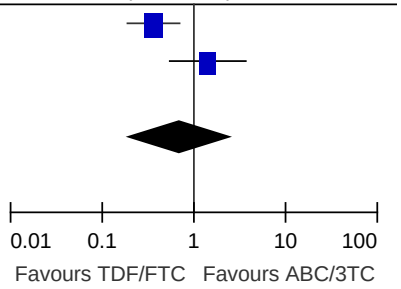
Favours TDF/FTC.

Proportion with grade 3/4 triglycerides

Study or Subgroup	TDF/FTC Events	TDF/FTC Total	ABC/3TC Events	ABC/3TC Total	Weight	Risk Ratio M-H, Random, 95% CI
Daar 2011 (ACTG5202)	12	925	33	923	53.4%	0.36 [0.19, 0.70]
Smith 2009 (HEAT)	10	345	7	343	46.6%	1.42 [0.55, 3.69]
Total (95% CI)		**1270**		**1266**	**100.0%**	**0.69 [0.18, 2.61]**
Total events	22		40			

Heterogeneity: Tau² = 0.76; Chi² = 5.35, df = 1 (P = 0.02); I² = 81%

Test for overall effect: Z = 0.55 (P = 0.58)



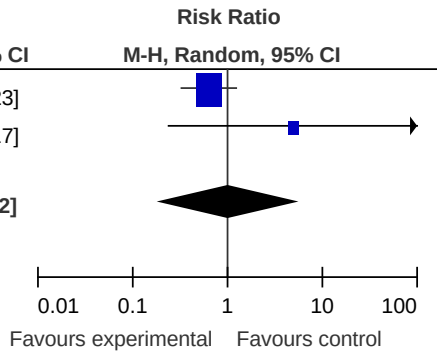
No clear evidence of a difference between the treatment arms.

Renal failure

Study or Subgroup	TDF/FTC Events	TDF/FTC Total	ABC/3TC Events	ABC/3TC Total	Weight	Risk Ratio M-H, Random, 95% CI
Sax 2011 (ACTG5202)	14	929	22	928	76.6%	0.64 [0.33, 1.23]
Smith 2009 (HEAT)	2	345	0	343	23.4%	4.97 [0.24, 103.17]
Total (95% CI)		**1274**		**1271**	**100.0%**	**1.03 [0.18, 5.72]**
Total events	16		22			

Heterogeneity: Tau² = 0.89; Chi² = 1.71, df = 1 (P = 0.19); I² = 41%

Test for overall effect: Z = 0.03 (P = 0.97)



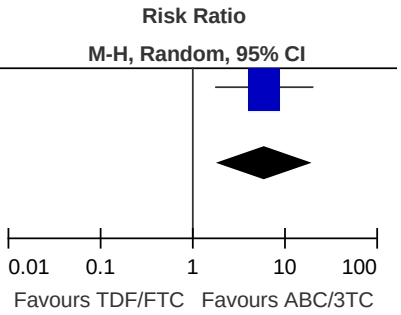
No clear evidence of a difference between the treatment arms.

Chronic toxicities (bone): % with total hip BMD decrease 6% or more at week 48.

	TDF/FTC		ABC/3TC			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
Post 2010 (ASSERT)	18	193	3	192	100.0%	5.97 [1.79, 19.93]
Total (95% CI)		**193**		**192**	**100.0%**	**5.97 [1.79, 19.93]**
Total events	18		3			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.90 (P = 0.004)

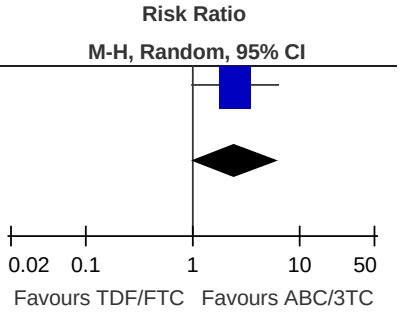


% with total spine BMD decrease 6% or more at week 48.

	TDF/FTC		ABC/3TC			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
Post 2010 (ASSERT)	15	193	6	192	100.0%	2.49 [0.99, 6.27]
Total (95% CI)		**193**		**192**	**100.0%**	**2.49 [0.99, 6.27]**
Total events	15		6			

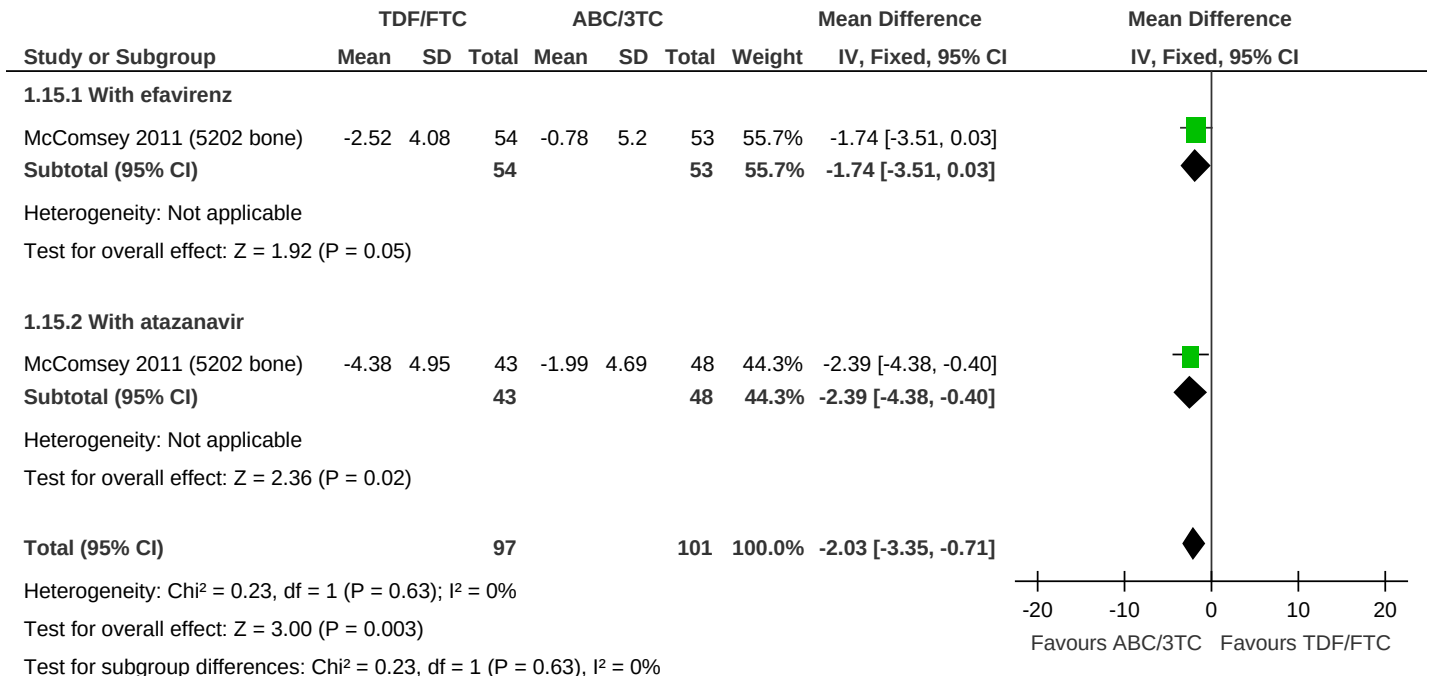
Heterogeneity: Not applicable

Test for overall effect: Z = 1.93 (P = 0.05)

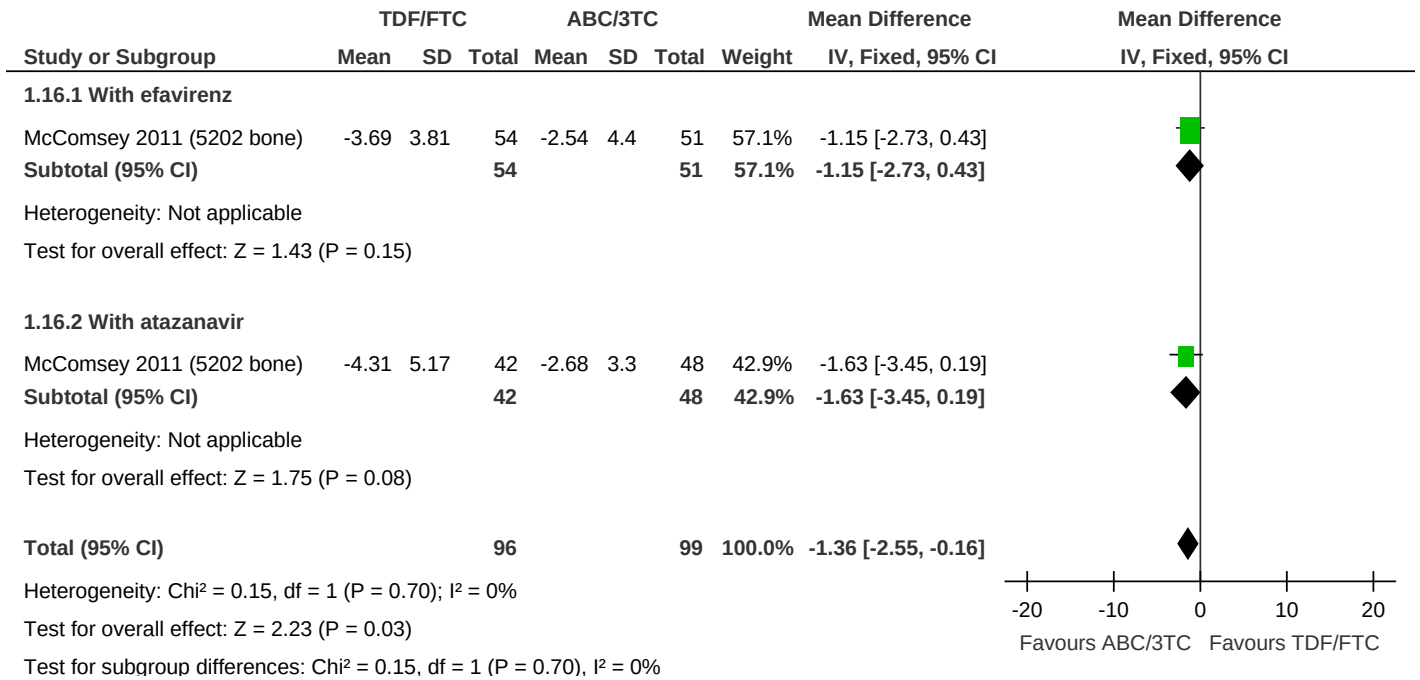


These both suggest that there is less bone loss with ABC/3TC, but is the decrease of 6% a) a recognised cut-off point? b) clinically significant?

Change in lumbar spine BMD (%, week 96).



Change in hip BMD (%, week 96).



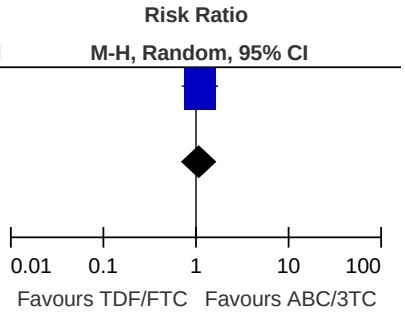
Equally, is a difference of 1-2% in the change in BMD significant?

Bone fractures

Study or Subgroup	TDF/FTC Events	TDF/FTC Total	ABC/3TC Events	ABC/3TC Total	Weight	Risk Ratio M-H, Random, 95% CI
Daar 2011 (ACTG5202)	42	925	38	923	100.0%	1.10 [0.72, 1.69]
Total (95% CI)		**925**		**923**	**100.0%**	**1.10 [0.72, 1.69]**
Total events	42		38			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.45 (P = 0.65)



Suggests no difference between groups.

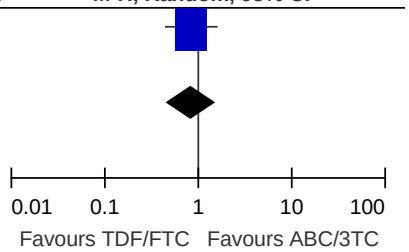
Lipodystrophy outcomes

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

Study or Subgroup	TDF/FTC Events	TDF/FTC Total	ABC/3TC Events	ABC/3TC Total	Weight	Risk Ratio M-H, Random, 95% CI
McComsey 2011 (5202 lipo)	15	101	18	102	100.0%	0.84 [0.45, 1.58]
Total (95% CI)		**101**		**102**	**100.0%**	**0.84 [0.45, 1.58]**
Total events	15		18			

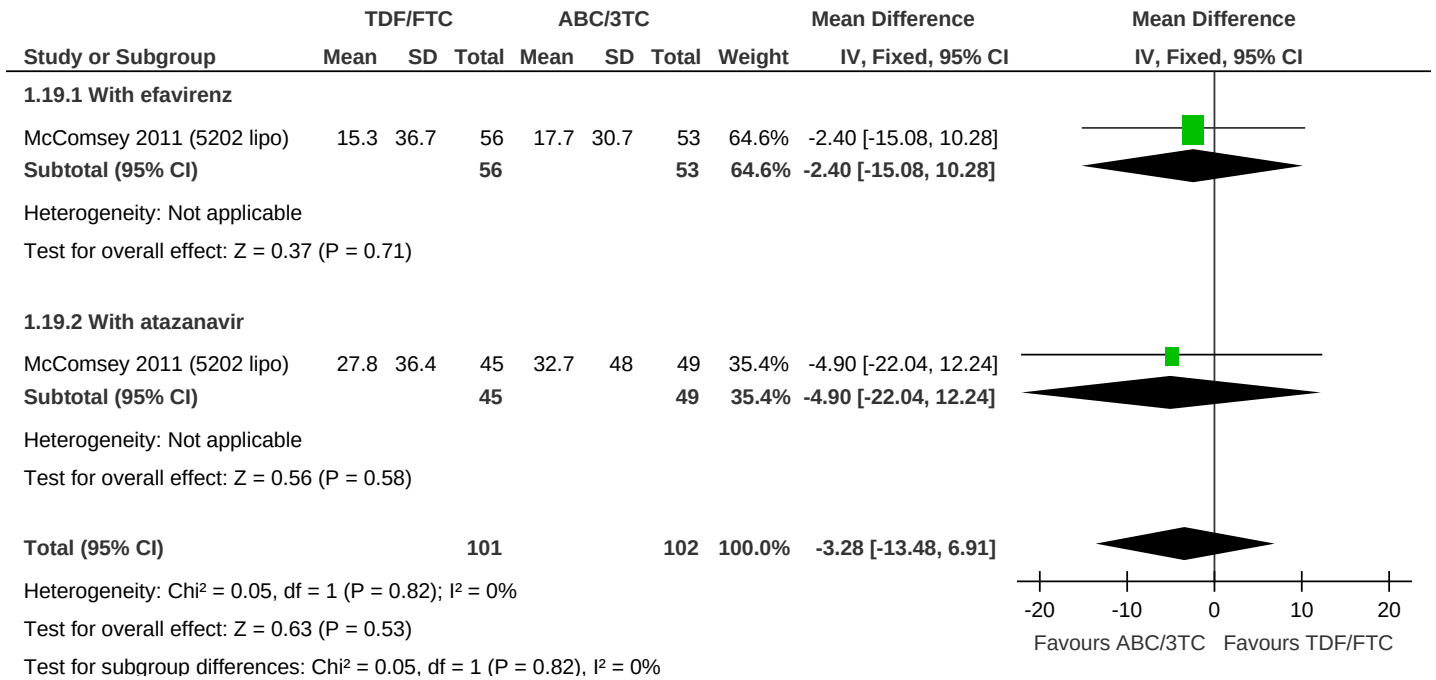
Heterogeneity: Not applicable

Test for overall effect: Z = 0.54 (P = 0.59)



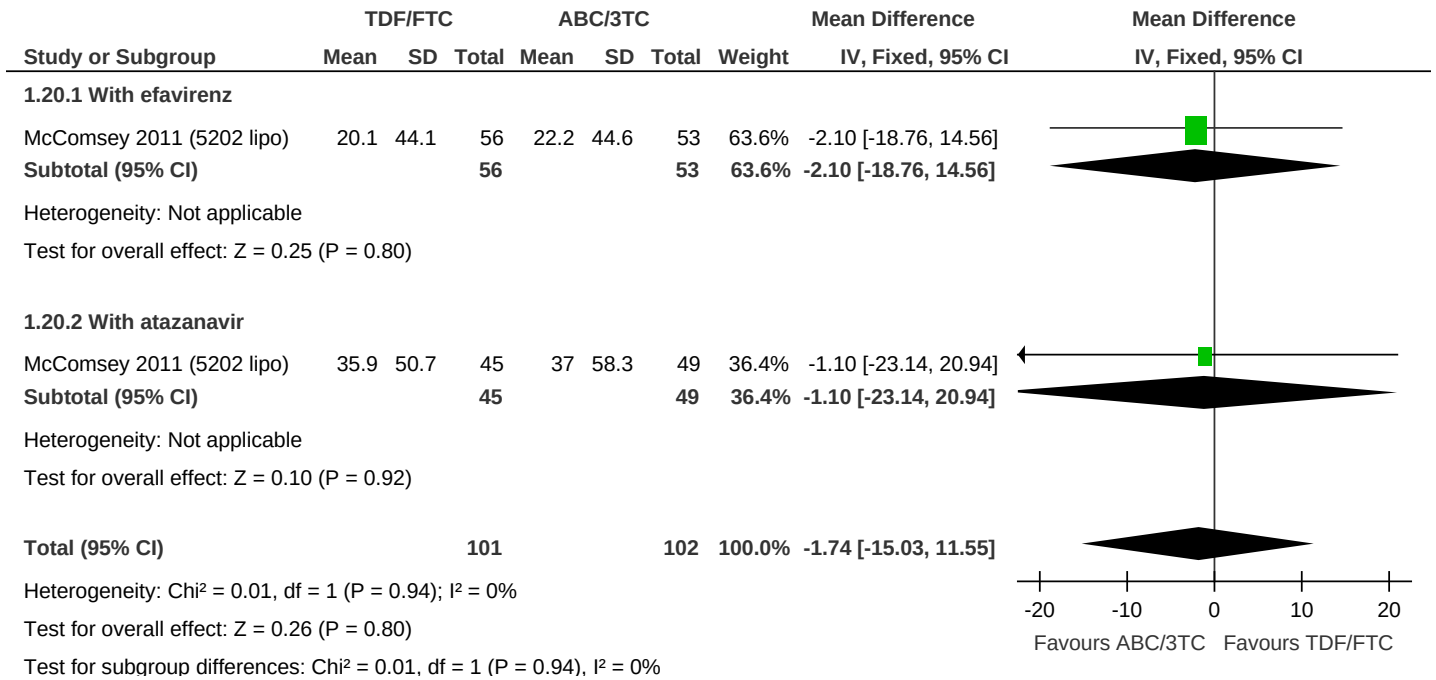
Suggests no difference between groups.

Change in limb fat (%, week 96).



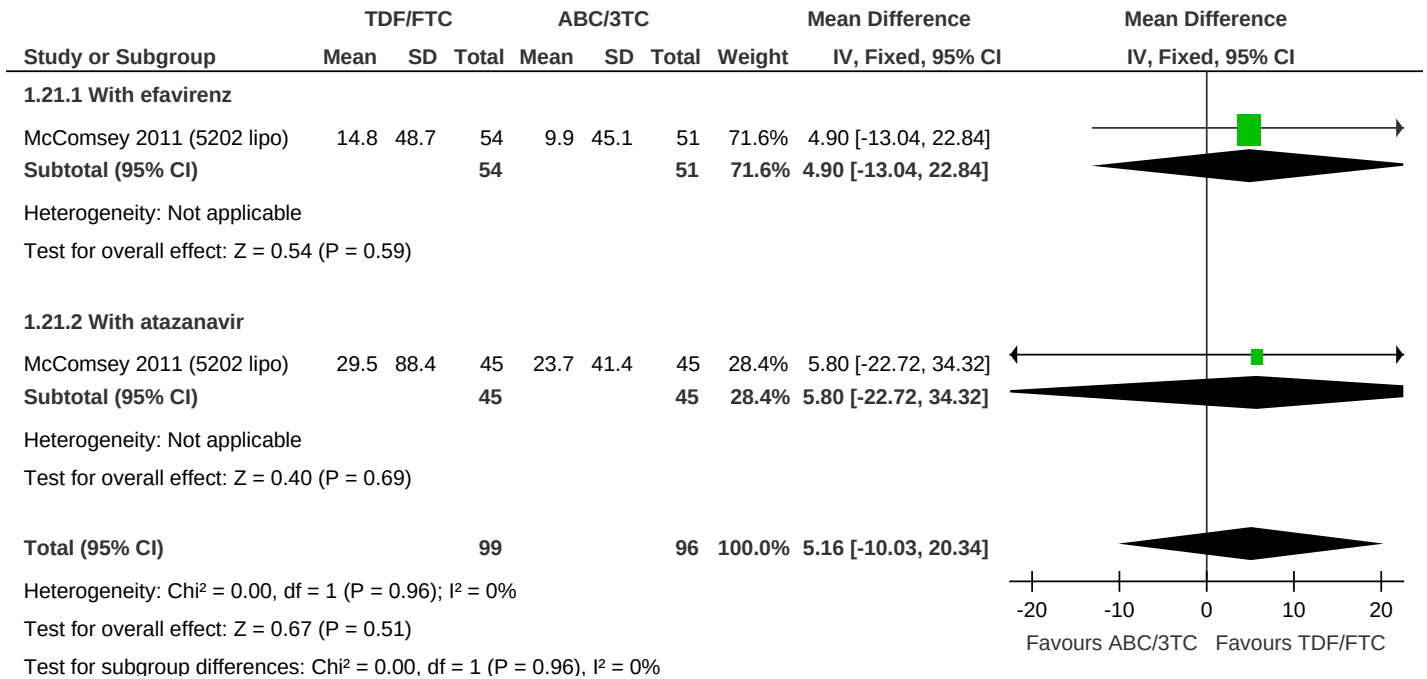
Suggests no difference between groups.

Change in trunk fat (%, week 96).



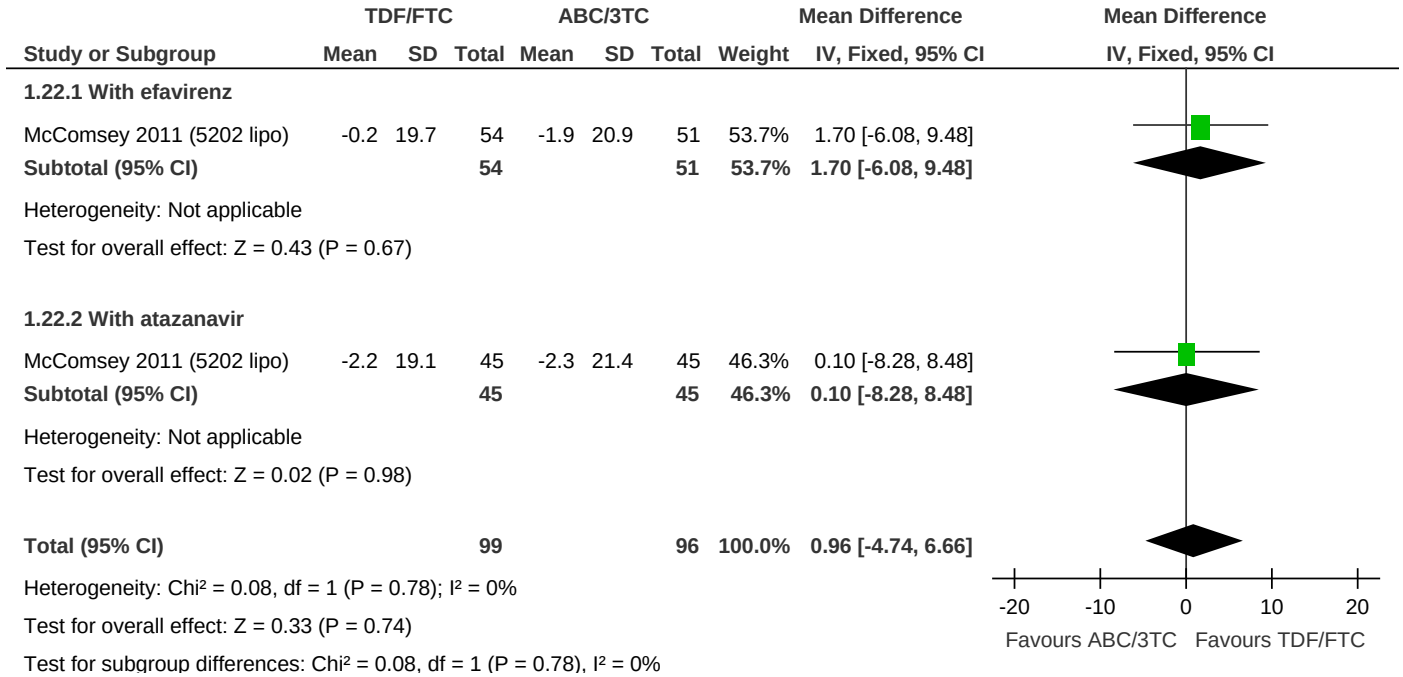
Suggests no difference between groups.

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



Suggests no difference between groups.

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



Suggests no difference between groups.

GRADE table:

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	TDF/FTC versus ABC/3TC	control	Relative (95% CI)	Absolute		
Virological suppression - <50 copies at 48 weeks (follow-up 48 weeks)												
2	randomised trials	very serious[1,2]	serious[3]	no serious indirectness	no serious imprecision	none	368/538 (68.4%)	346/535 (64.7%) 63.5%	RR 1.08 (0.9 to 1.3)	52 more per 1000 (from 65 fewer to 194 more) 51 more per 1000 (from 64 fewer to 190 more)	⊕OOO VERY LOW	CRITICAL
Virological suppression - <50 copies at 96 weeks (follow-up 96 weeks)												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	200/345 (58%)	205/343 (59.8%) 59.8%	RR 0.97 (0.86 to 1.1)	18 fewer per 1000 (from 84 fewer to 60 more) 18 fewer per 1000 (from 84 fewer to 60 more)	⊕⊕OO LOW	CRITICAL
Virological failure (all pts) - 48 weeks (follow-up 48 weeks)												
3	randomised trials	very serious[1,2]	serious[3]	no serious indirectness	no serious imprecision	none	138/1467 (9.4%)	186/1463 (12.7%) 14.1%	RR 0.76 (0.53 to 1.07)	31 fewer per 1000 (from 60 fewer to 9 more) 34 fewer per 1000 (from 66 fewer to 10 more)	⊕OOO VERY LOW	CRITICAL
Virological failure (all pts) - 96 weeks (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	114/925 (12.3%)	155/923 (16.8%)	RR 0.73 (0.59 to 0.92)	45 fewer per 1000 (from 13 fewer to 69 fewer)	⊕⊕⊕⊕	CRITICAL

								16.8%		45 fewer per 1000 (from 13 fewer to 69 fewer)	HIGH	
Drug resistance (follow-up 96 weeks)												
3	randomised trials	very serious[1,2]	serious[3]	no serious indirectness	no serious imprecision	none	49/1463 (3.3%)	67/1458 (4.6%) 3.2%	RR 0.79 (0.33 to 1.9)	10 fewer per 1000 (from 31 fewer to 41 more) 7 fewer per 1000 (from 21 fewer to 29 more)	⊕OOO VERY LOW	CRITICAL
Patients discontinuing for adverse events (follow-up 96 weeks)												
2	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42/538 (7.8%)	44/535 (8.2%) 9.3%	RR 0.94 (0.63 to 1.42)	5 fewer per 1000 (from 30 fewer to 35 more) 6 fewer per 1000 (from 34 fewer to 39 more)	⊕⊕OO LOW	CRITICAL
Grade 3-4 adverse events (any) - 96 weeks (follow-up 96 weeks)												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	97/345 (28.1%)	103/343 (30%) 30%	RR 0.94 (0.74 to 1.18)	18 fewer per 1000 (from 78 fewer to 54 more) 18 fewer per 1000 (from 78 fewer to 54 more)	⊕⊕OO LOW	CRITICAL
Grade 3-4 adverse events (any) - At end of follow up												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	257/923 (27.8%)	288/925 (31.1%) 31.1%	RR 0.89 (0.78 to 1.03)	34 fewer per 1000 (from 68 fewer to 9 more) 34 fewer per 1000 (from 68 fewer to 9 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Grade 3-4 neurological event (follow-up 96 weeks)												
1	randomised	no serious	no serious	no serious	no serious	none	38/925 (4.1%)	42/923	RR 0.9 (0.59 to	5 fewer per 1000 (from 19	⊕⊕⊕⊕	IMPORTANT

	trials	limitations	inconsistency	indirectness	imprecision			(4.6%) 4.6%	1.39)	fewer to 18 more) 5 fewer per 1000 (from 19 fewer to 18 more)	HIGH	
Grade 3-4 diarrhoea (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/925 (1.8%)	18/923 (2%) 2%	RR 0.94 (0.49 to 1.82)	1 fewer per 1000 (from 10 fewer to 16 more) 1 fewer per 1000 (from 10 fewer to 16 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Grade 3-4 ALT/AST elevation (follow-up 96 weeks)												
2	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/1264 (2.4%)	46/1263 (3.6%) 3.2%	RR 0.65 (0.41 to 1.03)	13 fewer per 1000 (from 21 fewer to 1 more) 11 fewer per 1000 (from 19 fewer to 1 more)	⊕⊕OO LOW	CRITICAL
Grade 3-4 increased total cholesterol (follow-up 96 weeks)												
2	randomised trials	very serious[1,2]	serious[3]	no serious indirectness	no serious imprecision	none	12/1270 (0.9%)	35/1266 (2.8%) 2.2%	RR 0.43 (0.13 to 1.39)	16 fewer per 1000 (from 24 fewer to 11 more) 13 fewer per 1000 (from 19 fewer to 9 more)	⊕OOO VERY LOW	NOT IMPORTANT
Grade 3-4 LDL cholesterol (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/925 (2.4%)	43/923 (4.7%) 4.7%	RR 0.51 (0.31 to 0.85)	23 fewer per 1000 (from 7 fewer to 32 fewer) 23 fewer per 1000 (from 7 fewer to 32 fewer)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Grade 3-4 increased triglycerides (follow-up 96 weeks)												

2	randomised trials	very serious[1,2]	serious[3]	no serious indirectness	no serious imprecision	none	22/1270 (1.7%)	40/1266 (3.2%) 2.8%	RR 0.69 (0.18 to 2.61)	10 fewer per 1000 (from 26 fewer to 51 more) 9 fewer per 1000 (from 23 fewer to 45 more)	⊕OOO VERY LOW	NOT IMPORTANT
Renal failure (follow-up 96 weeks)												
2	randomised trials	very serious[1,2]	serious[3]	no serious indirectness	no serious imprecision	none	16/1274 (1.3%)	22/1271 (1.7%) 1.2%	RR 1.03 (0.18 to 5.72)	1 more per 1000 (from 14 fewer to 82 more) 0 more per 1000 (from 10 fewer to 57 more)	⊕OOO VERY LOW	IMPORTANT
% with total hip BMD decrease 6% or more at week 48 (follow-up 48 weeks)												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/193 (9.3%)	3/192 (1.6%) 1.6%	RR 5.97 (1.79 to 19.93)	78 more per 1000 (from 12 more to 296 more) 80 more per 1000 (from 13 more to 303 more)	⊕⊕OO LOW	NOT IMPORTANT
% with total spine BMD decrease 6% or more at week 48 (follow-up 48 weeks)												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/193 (7.8%)	6/192 (3.1%) 3.1%	RR 2.49 (0.99 to 6.27)	47 more per 1000 (from 0 fewer to 165 more) 46 more per 1000 (from 0 fewer to 163 more)	⊕⊕OO LOW	NOT IMPORTANT
Change in lumbar spine BMD (%, week 96) (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	97	101	-	MD 2.03 lower (3.35 to 0.71 lower)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Change in lumbar spine BMD (%, week 96) - With efavirenz (follow-up 96 weeks; Better indicated by higher values)												
1	randomised	no serious	no serious	no serious	no serious	none	54	53	-	MD 1.74 lower (3.51	⊕⊕⊕⊕	NOT

	trials	limitations	inconsistency	indirectness	imprecision					lower to 0.03 higher)	HIGH	IMPORTANT
Change in lumbar spine BMD (%, week 96) - With atazanavir (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	43	48	-	MD 2.39 lower (4.38 to 0.4 lower)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Change in hip BMD (%, week 96) (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	96	99	-	MD 1.36 lower (2.55 to 0.16 lower)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Change in hip BMD (%, week 96) - With efavirenz (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	54	51	-	MD 1.15 lower (2.73 lower to 0.43 higher)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Change in hip BMD (%, week 96) - With atazanavir (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	42	48	-	MD 1.63 lower (3.45 lower to 0.19 higher)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Bone fractures (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	42/925 (4.5%)	38/923 (4.1%) 4.1%	RR 1.1 (0.72 to 1.69)	4 more per 1000 (from 12 fewer to 28 more) 4 more per 1000 (from 11 fewer to 28 more)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Patients with 10% or more limb fat loss (week 96) (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/101 (14.9%)	18/102 (17.6%) 17.7%	RR 0.84 (0.45 to 1.58)	28 fewer per 1000 (from 97 fewer to 102 more) 28 fewer per 1000 (from 97 fewer to 103 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

Change in limb fat (%, week 96) (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[4]	none	101	102	-	MD 3.28 lower (13.48 lower to 6.91 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Change in limb fat (%, week 96) - With efavirenz (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[4]	none	56	53	-	MD 2.4 lower (15.08 lower to 10.28 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Change in limb fat (%, week 96) - With atazanavir (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[4]	none	45	49	-	MD 4.9 lower (22.04 lower to 12.24 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Change in trunk fat (%, week 96) (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[4]	none	101	102	-	MD 1.74 lower (15.03 lower to 11.55 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Change in trunk fat (%, week 96) - With efavirenz (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[4]	none	56	53	-	MD 2.1 lower (18.76 lower to 14.56 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Change in trunk fat (%, week 96) - With atazanavir (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[4]	none	45	49	-	MD 1.1 lower (23.14 lower to 20.94 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Change in visceral adipose tissue (VAT; %, week 96) (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[4]	none	99	96	-	MD 5.16 higher (10.03 lower to 20.34 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Change in visceral adipose tissue (VAT; %, week 96) - With efavirenz (follow-up 96 weeks; Better indicated by higher values)												

1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[4]	none	54	51	-	MD 4.9 higher (13.04 lower to 22.84 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Change in visceral adipose tissue (VAT; %, week 96) - With atazanavir (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[4]	none	45	45	-	MD 5.8 higher (22.72 lower to 34.32 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Change in visceral:total adipose tissue (VAT:TAT; %, week 96) (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[4]	none	99	96	-	MD 0.96 higher (4.74 lower to 6.66 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Change in visceral:total adipose tissue (VAT:TAT; %, week 96) - With efavirenz (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[4]	none	54	51	-	MD 1.7 higher (6.08 lower to 9.48 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Change in visceral:total adipose tissue (VAT:TAT; %, week 96) - With atazanavir (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[4]	none	45	45	-	MD 0.1 higher (8.28 lower to 8.48 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Drug-related adverse events grades 2-4 (follow-up 96 weeks)												
2	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42/538 (7.8%)	44/535 (8.2%) 9.3%	RR 0.94 (0.63 to 1.42)	5 fewer per 1000 (from 30 fewer to 35 more) 6 fewer per 1000 (from 34 fewer to 39 more)	⊕⊕OO LOW	CRITICAL

[1] Randomisation method and allocation concealment unclear
[2] High drop out
[3] Heterogeneity between studies
[4] Wide confidence intervals