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Speaker Name	Statement
Dr Andrew Hill	Andrew Hill has received consultancy payments from Gilead, Bristol-Myers Squibb, Janssen and ViiV, not connected with this project.
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No difference in risk of virological failure between antiretroviral treatments using co-formulated versus individual drugs: meta-analysis of 9 randomised trials in 2,568 patients

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Background

Non-randomised cohort studies have shown conflicting evidence on the potential benefits of using fixed-dose combinations of antiretrovirals (FDCs). Cohort studies can give misleading results because of biases in patient selection.

Randomised head-to-head studies are the most reliable method to assess efficacy and safety, and are given the highest grading of evidence to support international treatment guidelines.

Research question: Does the use of co-formulated ARV's improve efficacy in randomised head-to-head trials?

Is there an efficacy benefit to STR's to justify their much higher price than individual generic pills?

Single pill
£4500 - £7400/year*

TDF/FTC/EFV

TDF/FTC/RPV

TDF/FTC/ELV/c

ABC/3TC/DTG

Three pills
<£1000/year

Generic ABC or TDF

Generic 3TC

Generic EFV or PI/r

***Prices include 30% discount from NHS list price (BNF)**
Sources: BNF 2014, generic company prices

Methods

A systematic PUBMED/EMBASE search identified open-label randomised trials comparing co-formulated antiretrovirals with individual components

These were divided into two groups:

Group 1: Older trials comparing co-formulations with individual drugs

e.g. ABC/3TC versus ABC + 3TC

Group 2: Comparisons of single tablets (1/day) versus combinations (2-3/day)

e.g. TDF/FTC/ELV/c versus 2NRTI + PI/r

Group 1: Five co-formulation trials

Trial / Inclusion	N	Duration	Design	Pill counts
Eron 1998 (Switch)	223	16 weeks	ZDV/3TC + PI	7
			ZDV+3TC + PI	9
SEAL 2005 (Switch)	260	48 weeks	ABC/3TC + PI or NNRTI	3
			ABC+3TC + PI or NNRTI	6
Fischl 2003 (Switch)	196	24 weeks	ZDV/3TC/ABC (Trizivir)	2
			ZDV/3TC + ABC	4
CAL30001 2006 (VF)	186	48 weeks	ABC/3TC +TDF+ PI or NNRTI	5
			ABC+3TC +TDF+PI or NNRTI	7
EZ Switch 2008 (Switch)	94	8 weeks	ABC/3TC + PI or NNRTI	3
			ABC + 3TC + PI or NNRTI	5

Group 2: Four STR trials (1 vs 3 pills/day)

Trial / Inclusion	N	Duration	Design / pill counts	
STRATEGY-PI (Switch)	433	48 weeks	TDF/FTC/ELV/c	2NRTI+PI/r
SPIRIT (Switch)	476	24 weeks	TDF/FTC/RPV	2NRTI+PI/r
A1266703 (Switch)	300	48 weeks	TDF/FTC/EFV	2NRTI+SOC
STRATEGY-NNRTI (Switch)	434	48 weeks	TDF/FTC/ELV/c	2NRTI+NNRTI*

* In STRATEGY-NNRTI, 80% taking Atripla, 4% Complera, 15% NVP, 1% ETR: 1-3 pills day

Statistical Methods

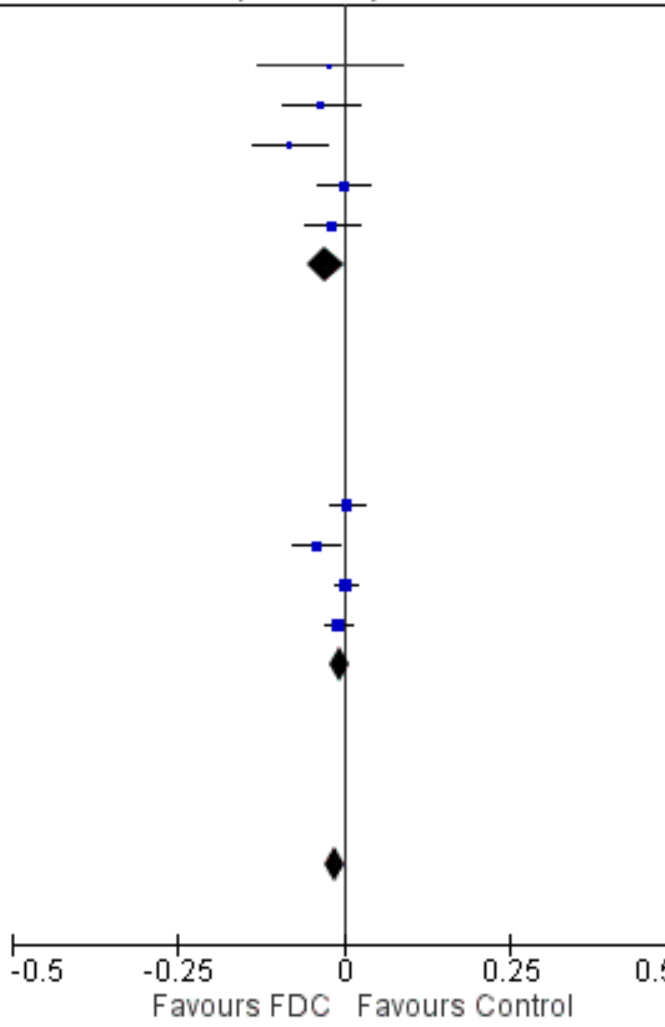
Efficacy and safety was compared between the co-formulated and separate components using five endpoints, using meta-analysis with inverse-variance weighting:

- Virological failure: HIV RNA >400 copies/mL
- Treatment-emergent resistance
- Discontinuation for adverse events
- Discontinuation for other reasons (TLOVR)
- Treatment adherence

The two groups of trials were analysed individually and then combined.

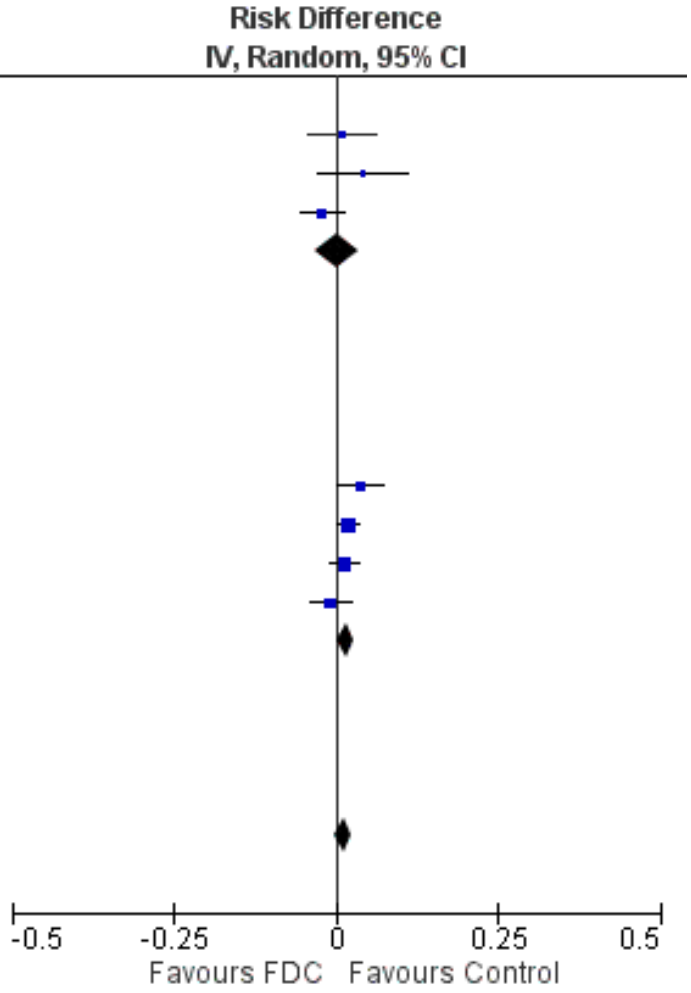
Meta-analysis: Virological Failure endpoint. 1% lower for FDCs (95% CI: -2.8%, +0.2%)

Study or Subgroup	FDC Events	FDC Total	Control Events	Control Total	Weight	Risk Difference IV, Random, 95% CI
1.2.1 Group 1						
CAL30001	14	88	17	94	1.8%	-0.0218 [-0.1308, 0.0873]
Eron	4	110	8	113	5.4%	-0.0344 [-0.0933, 0.0244]
ESS40005	0	97	8	98	5.7%	-0.0816 [-0.1386, -0.0247]
EZ Switch	0	47	0	47	9.5%	0.0000 [-0.0406, 0.0406]
SEAL	2	119	4	117	9.6%	-0.0174 [-0.0576, 0.0228]
Subtotal (95% CI)		**461**		**469**	**32.0%**	**-0.0273 [-0.0553, 0.0007]**
Total events	20		37			
Heterogeneity: Tau² = 0.00; Chi² = 5.49, df = 4 (P = 0.24); I² = 27%						
Test for overall effect: Z = 1.91 (P = 0.06)						
1.2.2 Group 2						
A1266073	3	203	1	97	16.1%	0.0045 [-0.0216, 0.0305]
SPIRIT	3	317	8	159	11.3%	-0.0409 [-0.0765, -0.0052]
STRATEGY-NNRTI	3	290	1	143	21.7%	0.0034 [-0.0146, 0.0213]
STRATEGY-PI	2	290	2	139	18.8%	-0.0075 [-0.0295, 0.0145]
Subtotal (95% CI)		**1100**		**538**	**68.0%**	**-0.0061 [-0.0221, 0.0099]**
Total events	11		12			
Heterogeneity: Tau² = 0.00; Chi² = 5.26, df = 3 (P = 0.15); I² = 43%						
Test for overall effect: Z = 0.74 (P = 0.46)						
Total (95% CI)		**1561**		**1007**	**100.0%**	**-0.0131 [-0.0281, 0.0018]**
Total events	31		49			
Heterogeneity: Tau² = 0.00; Chi² = 13.30, df = 8 (P = 0.10); I² = 40%						
Test for overall effect: Z = 1.72 (P = 0.09)						
Test for subgroup differences: Chi² = 1.66, df = 1 (P = 0.20), I² = 39.7%						



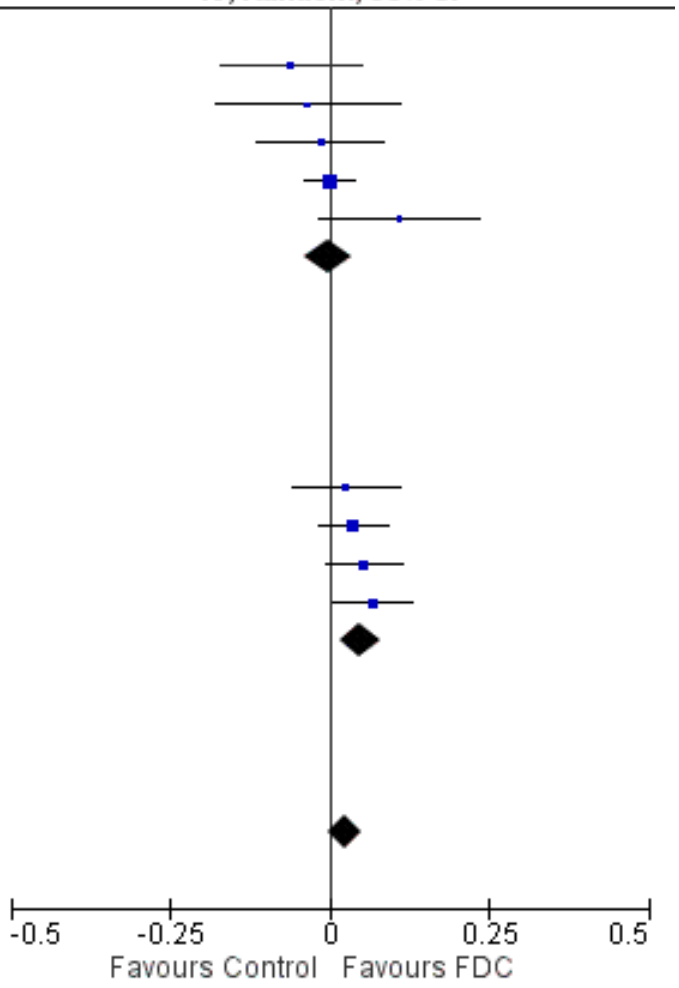
Meta-analysis, Discontinuation for AEs
1% higher for FDCs (95% CI: -0.2%, +2.6%)

Study or Subgroup	FDC Events	FDC Total	Control Events	Control Total	Weight	Risk Difference IV, Random, 95% CI
1.4.1 Group 1						
Eron	5	110	4	113	6.4%	0.0101 [-0.0417, 0.0618]
EZ Switch	2	47	0	47	3.8%	0.0426 [-0.0266, 0.1117]
SEAL	0	99	2	99	13.0%	-0.0202 [-0.0538, 0.0134]
Subtotal (95% CI)		**256**		**259**	**23.2%**	**0.0010 [-0.0328, 0.0349]**
Total events	7		6			
Heterogeneity: Tau² = 0.00; Chi² = 2.92, df = 2 (P = 0.23); I² = 32%						
Test for overall effect: Z = 0.06 (P = 0.95)						
1.4.2 Group 2						
A1266073	10	203	1	97	11.7%	0.0390 [0.0030, 0.0749]
SPIRIT	6	317	0	159	27.8%	0.0189 [0.0011, 0.0367]
STRATEGY-NNRTI	6	291	1	143	23.3%	0.0136 [-0.0077, 0.0349]
STRATEGY-PI	6	293	4	140	13.9%	-0.0081 [-0.0401, 0.0239]
Subtotal (95% CI)		**1104**		**539**	**76.8%**	**0.0156 [0.0015, 0.0296]**
Total events	28		6			
Heterogeneity: Tau² = 0.00; Chi² = 3.89, df = 3 (P = 0.27); I² = 23%						
Test for overall effect: Z = 2.17 (P = 0.03)						
Total (95% CI)		**1360**		**798**	**100.0%**	**0.0115 [-0.0025, 0.0256]**
Total events	35		12			
Heterogeneity: Tau² = 0.00; Chi² = 8.56, df = 6 (P = 0.20); I² = 30%						
Test for overall effect: Z = 1.61 (P = 0.11)						
Test for subgroup differences: Chi² = 0.60, df = 1 (P = 0.44), I² = 0%						



Meta-analysis: Switch=Failure endpoint: 2.6% lower for FDCs (95% CI: +0.4%, -5.1%)

Study or Subgroup	FDC Events	FDC Total	Control Events	Control Total	Weight	Risk Difference IV, Random, 95% CI
1.1.1 Group 1						
Eron	81	110	90	113	5.2%	-0.0601 [-0.1710, 0.0508]
CAL30001	41	88	47	94	3.1%	-0.0341 [-0.1793, 0.1111]
SEAL	96	119	96	117	6.3%	-0.0138 [-0.1131, 0.0856]
EZ Switch	47	47	47	47	26.2%	0.0000 [-0.0406, 0.0406]
ESS40005	74	97	64	98	4.0%	0.1098 [-0.0168, 0.2365]
Subtotal (95% CI)		**461**		**469**	**44.9%**	**-0.0013 [-0.0387, 0.0361]**
Total events	339		344			
Heterogeneity: Tau² = 0.00; Chi² = 4.30, df = 4 (P = 0.37); I² = 7%						
Test for overall effect: Z = 0.07 (P = 0.94)						
1.1.2 Group 2						
A1266073	177	203	82	97	8.3%	0.0266 [-0.0588, 0.1119]
SPIRIT	297	317	143	159	17.7%	0.0375 [-0.0163, 0.0914]
STRATEGY-NNRTI	271	290	126	143	14.9%	0.0534 [-0.0068, 0.1136]
STRATEGY-PI	272	290	121	139	14.1%	0.0674 [0.0051, 0.1298]
Subtotal (95% CI)		**1100**		**538**	**55.1%**	**0.0479 [0.0165, 0.0793]**
Total events	1017		472			
Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 3 (P = 0.85); I² = 0%						
Test for overall effect: Z = 2.99 (P = 0.003)						
Total (95% CI)		**1561**		**1007**	**100.0%**	**0.0258 [-0.0004, 0.0519]**
Total events	1356		816			
Heterogeneity: Tau² = 0.00; Chi² = 9.50, df = 8 (P = 0.30); I² = 16%						
Test for overall effect: Z = 1.93 (P = 0.05)						
Test for subgroup differences: Chi² = 3.91, df = 1 (P = 0.05), I² = 74.4%						



Group 2: Four STR trials (1 vs 3 pills/day) virological failure

Trial	VF: HIV RNA >400	
	FDC	Control
STRATEGY-PI	2/290 (1%)	1/139 (1%)
SPIRIT	3/317 (1%)	8/159 (5%)
A1266703	3/203 (1%)	1/97 (1%)
STRATEGY-NNRTI	3/290 (1%)	1/143 (1%)
Difference	-1.3% (-2.8%. +0.2%)	
	No significant difference between STR and single pills	

Group 2: Four STR trials (1 vs 3 pills/day) virological failure or discontinuation

Trial	VF or switch endpoint	
	FDC	Control
STRATEGY-PI	18/290 (7%)	18/139 (13%)
SPIRIT	20/317 (6%)	16/159 (10%)
A1266703	26/203 (13%)	15/97 (15%)
STRATEGY-NNRTI	19/290 (7%)	17/143 (12%)
Difference	-4.8% (-1.7%, -7.9%) p=0.003, in favour of STR	

* Switch with HIV RNA <50 copies/mL – mainly for other reasons (not adverse events)

Group 2: Four STR trials (1 vs 3 pills/day) Treatment-emergent drug resistance

Trial	VF: HIV RNA >400	
	FDC	Control
STRATEGY-PI	0/290 (0%)	0/139 (0%)
SPIRIT	4/317 (1%)	1/159 (1%)
A1266703	2/203 (1%)	0/97 (0%)
STRATEGY-NNRTI	0/290 (1%)	0/143 (1%)
	6/1100	1/538
	No difference between STR and single pills	

Adherence and Quality of Life

Patient preference: In most trials, patients preferred to take the co-formulated tablets or STRs, compared to single pills.

Adherence: In Group 1 trials, patients were 5% more likely to be highly adherent to treatment (>95%). However this did not translate into a significantly lower rate of virological failure. In Group 2, adherence did not differ between arms in the A12663 trial. In SPIRIT trial, 3% difference in adherence between groups.

Quality of Life: In STRATEGY-PI and A12663 trials, no difference in Quality of Life (SF-36 score) between STR and control treatment.

Limitations

The five “Group 1” trials were conducted several years ago, and may not be representative of current clinical practice

The four “Group 2” trials of STR versus individual drugs were switch studies for people with HIV RNA suppression at baseline. No trial data in naives.

Patients enrolled in switch studies may already be used to taking multi-pill treatments. However they could be entering these studies to access STRs and this may explain higher rates of discontinuation in control arms.

Conclusions

In a meta-analysis of 9 randomised head-to-head clinical trials, there was no significant benefit of fixed dose combinations over individual drugs in terms of protocol-defined virological failure, drug resistance or discontinuation for adverse events.

However, people on fixed dose combinations were 2.6% less likely to switch treatment with HIV RNA suppression, and had 5% higher adherence. This did not translate into any significant benefit in terms of virological failure or drug resistance.

The benefit of fixed dose combinations over individual generic pills has not been proved in randomised clinical trials, despite large differences in costs.

Implications

Pharmaceutical companies have not conducted randomised trials to evaluate the potential benefits of using STRs versus individual drugs in naïve patients.

The only available evidence from switch studies suggests no benefit for STRs in terms of virological failure or drug resistance. Evidence from cohort studies is conflicting and subject to biases in patient selection.

Use of generic individual antiretrovirals could potentially save the NHS £1.25 billion over the next 5 years, compared with use of patented high-cost STRs.

The cost-effectiveness of STRs versus 2-3 pill combinations of generic ARVs has not been established.

British HIV Association

BHIVA

21st Annual Conference of the British HIV Association (BHIVA)

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