A Structured Treatment Interruption (STI) strategy of 12 week cycles on and off ART is clinically inferior to continuous therapy in patients with low CD4 counts before ART: a randomisation within the DART trial

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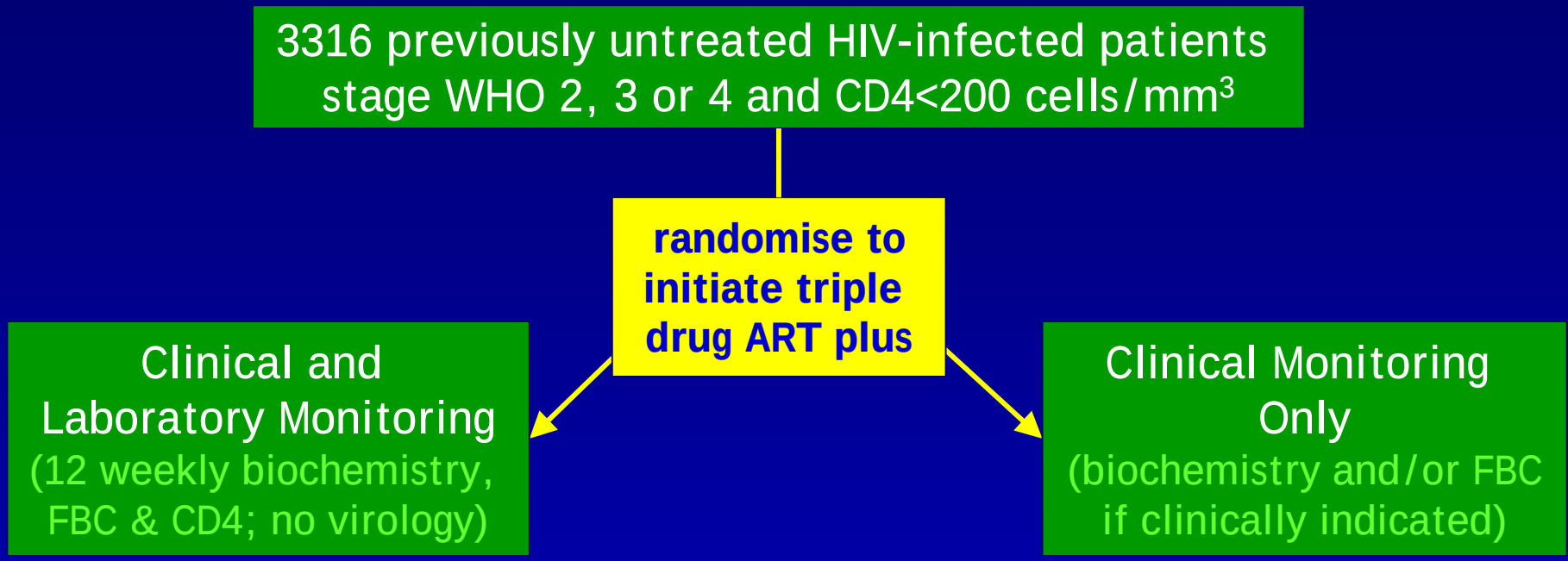
on behalf of the **DART** Trial Team

Background

- Intermittent therapy has the potential
  - to reduce long-term toxicity
  - to reduce ART costs
  - to improve adherence
- whilst maintaining clinical well-being
- One randomised trial in Africa has reported inferiority of a CD4-guided treatment interruption strategy (TRIVACAN)
- The feasibility of CD4-guided strategies may be limited by high CD4 variability

DART trial design: main randomisation



- Planned follow-up 4-5 years
- Primary endpoints
  - efficacy: new WHO 4 event or death
  - toxicity: Serious Adverse Events

STI trial design within DART

- A second randomisation in a subset of patients
  - same primary endpoints
- Patients with CD4≥300 cells/mm^3 after 48 or 72 weeks on ART were randomised to
  - STI (12 week cycles on/off treatment), or
  - continuous ART (CT)
- 813 eligible patients randomised between July 2004 and March 2006
- Following 2nd DSMC review in March 2006 based on data to mid-Jan 2006, the STI/CT randomisation was terminated on 15 March 2006, and all patients moved to continuous therapy

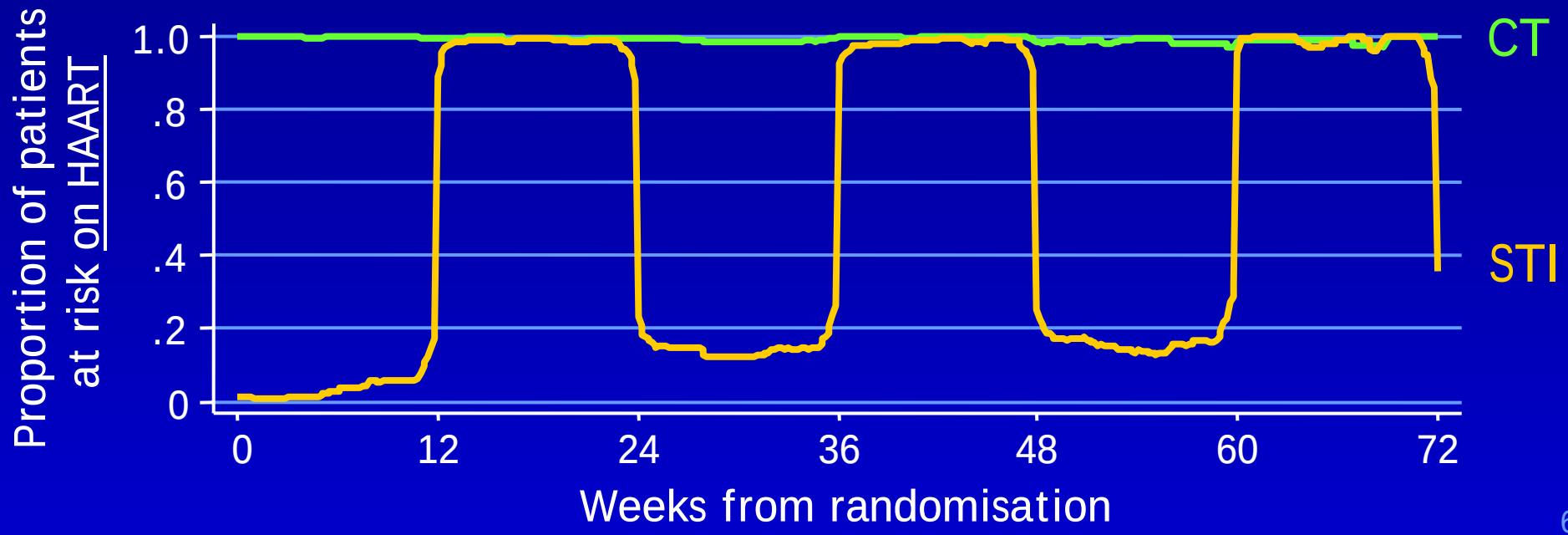
Characteristics at STI/CT randomisation

		CT	STI
Total patients		405	408
Weeks after starting ART	52 76	60% 40%	61% 39%
Women		74%	73%
Age (years)	median (range)	37 (19-63)	37 (21-67)
CD4 count (cells/mm^3) median	(range)	358 (300-819)	357 (300-1054)
CD4 nadir (cells/mm^3)	median (range)	128 (2-199)	136 (1-199)
ART: 2NRTIs plus	TDF ABC NVP *	68% 12% 20%	66% 9% 25%

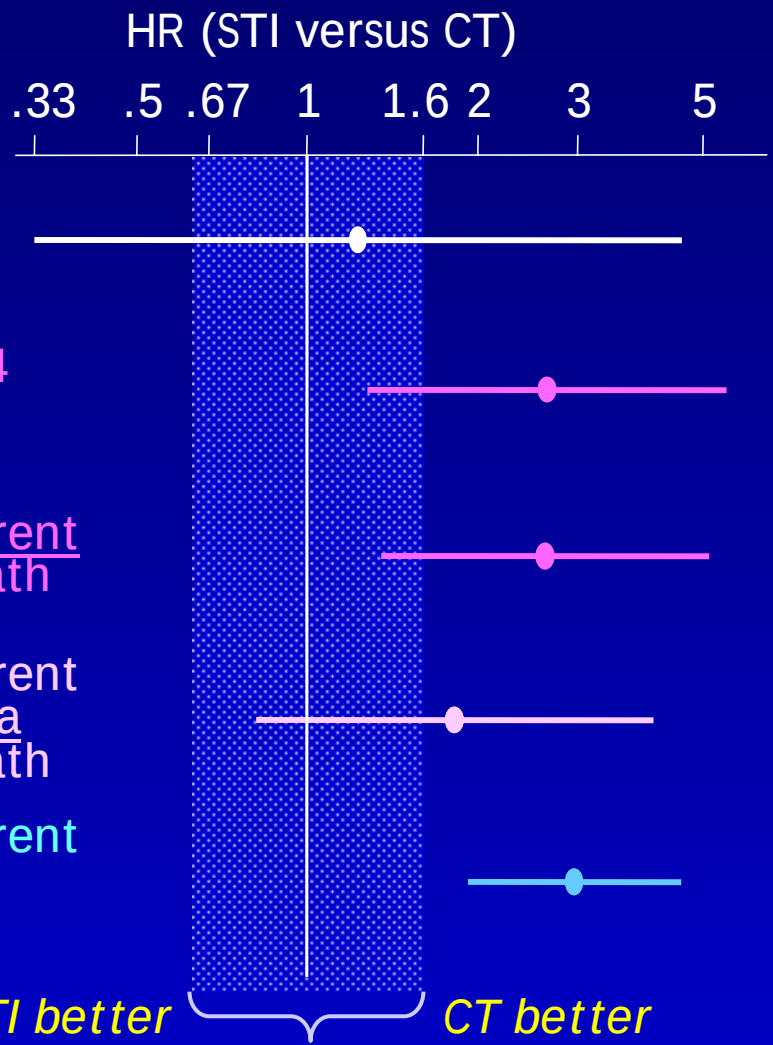
** all used a 7 day stagger stop*

Follow-up & ART received

- Median follow-up to 15 March 2006 51 weeks (IQR 37-64, range 0-85 weeks)
  - 99% of 386 PY in CT on triple drug ART
  - 50% of 388 PY in STI on triple drug ART
- 304/408 patients started 2 more STI cycles: max 4 cycles

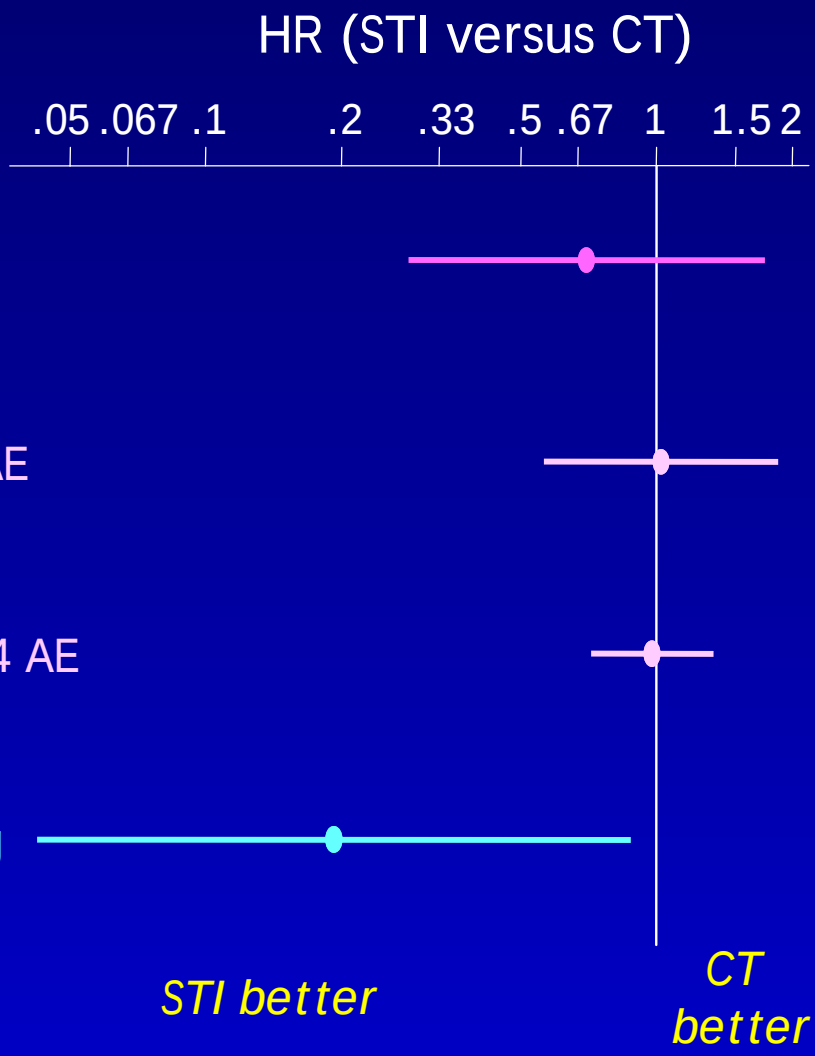


Summary of clinical outcome



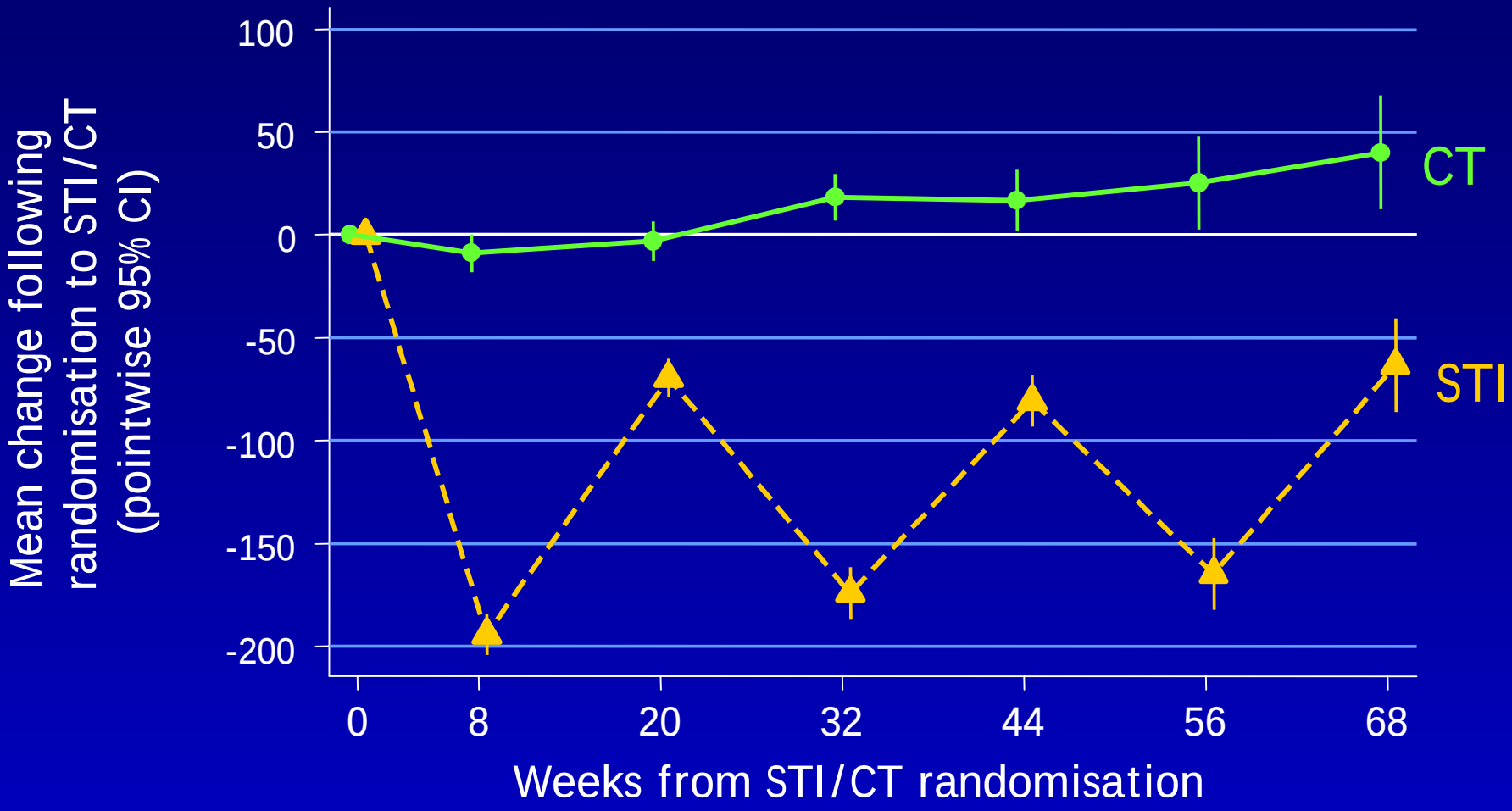
	STI: N (rate/100PY)	CT: N (rate/100PY)	HR	p
Death	5 (1.3)	4 (1.0)	1.30	0.70
1°: New WHO 4 /death	24 (6.4)	9 (2.4)	2.73	0.007
2°: New/recurrent WHO 4/death	30 (8.1)	12 (3.2)	2.58	0.004
New/recurrent non-candida WHO 4/death	14 (3.7)	8 (2.1)	1.78	0.19
New/recurrent WHO 3 or 4 or death	77 (22.4)	28 (7.6)	2.95	<0.001

Summary of reported AEs



	STI: N (rate/100 PY)	CT: N (rate/100 PY)	HR	p
1°: SAE	8 (2.1)	11 (2.9)	0.72	0.48
Grade 4 AE	22 (5.8)	21 (5.6)	0.96	0.91
2°: Grade 3/4 AE	79 (22.8)	79 (23.3)	0.97	0.82
ART-modifying AE	2 (0.5)	10 (2.6)	0.20	0.02

Change in CD4 count (ITT, secondary endpoint)



Numbers at risk

CT	405	395	380	328	257	151	74
STI	408	393	373	319	248	149	79

Conclusions

- Over median follow-up of 51 weeks, the majority of STI patients were able to take ART intermittently without developing WHO 4 events
- However, the STI strategy in DART was associated with a 2.6 fold increased rate of clinical WHO stage 4 events, and cannot therefore be recommended
  - no evidence of difference in mortality between STI and CT
- DART continues to follow-up patients to its primary goal of comparing different monitoring strategies

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DART

DART

First new WHO 4 event

	New		Additional recurrences	
	STI	CT	STI	CT
Oesoph candida	13	3	4	1
Ex pulm TB	4	1	0	0
Cryptococcosis	1	0	0	1
Herpes simplex	1	0	1	1
PCP	0	1	0	0
HIV wasting	0	0	1	0