BREATHER (PENTA 16)

BREaks in Adolescent and Child **TH**erapy using **E**favirenz and two n**R**tis

Phase II randomised trial to determine whether young people can maintain virological suppression during **Short Cycle Therapy (SCT) (5 days on/2 off)**

March 2011 – July 2014

Karina Butler on behalf of PENTA
(Paediatric European Network for the Treatment of AIDS)

Disclosures

Karina Butler
has no financial disclosures

Background & Rationale

- Aims of HIV treatment:
  - Maximise the benefit of ARVs/Minimise long-term toxicity
  - Maintain long-term adherence to prevent resistance and preserve future treatment options
- Challenges facing young people
  - Lifelong therapy
  - Adherence, including the social dimension (eg medication stigma, sleepovers, socialising at weekends, pill fatigue)

➢ **Need for new treatment strategies**

One Possible Option:

Short Cycle Therapy (SCT): 5 days on treatment / 2 days off

–Simplification with less toxicity

–Better adherence

–Cost savings

BREATHER: Global, Phase II, Randomised, Multi-center, Non-inferiority Trial

Hypothesis: **SCT is as efficacious as CT on EFV based 1st line therapy.**

Population: Aged 8 to 24 yrs, stable VL <50c/ml on EFV+2NRTI

- No previous virologic failure on a HAART regimen
- CD4 count ≥350 cells/μL at screening visit

Primary Outcome: Time to VL failure (HIV-1 RNA ≥50 c/ml, confirmed) over 48 wks

Pre-defined non inferiority margin: 12% *for the difference in failure rate between SCT and CT by week 48 (Kaplan-Meier), adjusted for age & geographic region*

Secondary outcomes:

- HIV < 50c/ml at 24 & 48 wks
- Change in CD4 at 24 & 48 wks
- New B, C events or death
- Adherence & acceptability over 48 wks
- Major HIV mutations
- Toxicities
- Change in ART

Enrolment

March 2011 – June 2013

199 Young people (YP), 11 countries

35% Uganda, 18% Thailand, 6% Argentina, 41% US & Europe

(32 in the pilot phase)

↓

RANDOMISATION

SCT	CT
99 YP (15 in pilot)	**100 YP (17 in pilot)**
Stop on Friday/Saturday OR Saturday/Sunday.	Continue taking ART 7 days a week

Study visits – week 4, 12, 24, 36, 48 and every 12 weeks to trial end

Baseline Characteristics

N:199:53% Male. Med age 14.1 (IQR: 11.9 – 17.6)
90% Vertically acquired. 56% Black, 21% White, 19% Asian

	SCT	CT	Total
Young people randomised: n	99	100	199
≥8 years to <13 years: n (%)	38 (38)	39 (39)	77 (39)
≥13 years to <18 years: n (%)	39 (39)	41 (41)	80 (40)
≥18 years to <24 years: n (%)	22 (22)	20 (20)	42 (21)
CDC Stage: n (%)			
N/A	41 (41)	35 (35)	76 (38)
B	45 (45)	43 (43)	88 (44)
C	13 (13)	21 (21)	34 (17)
CD4 %: median (IQR)	34.5 (29, 39)	34.0 (30, 38)	34.0 (30, 39)
CD4 absolute (cells/mm^3): median (IQR)	722.5 (581.0, 965.0)	747.3 (575.3, 972.8)	735.0 (575.5, 967.5)

Follow up: median 85.7 weeks, with >98% clinic visits attended up to week 48.
One lost to follow up by week 48 (relocated)

Adherence to Strategy

Three independent indicators confirmed adherence to strategy

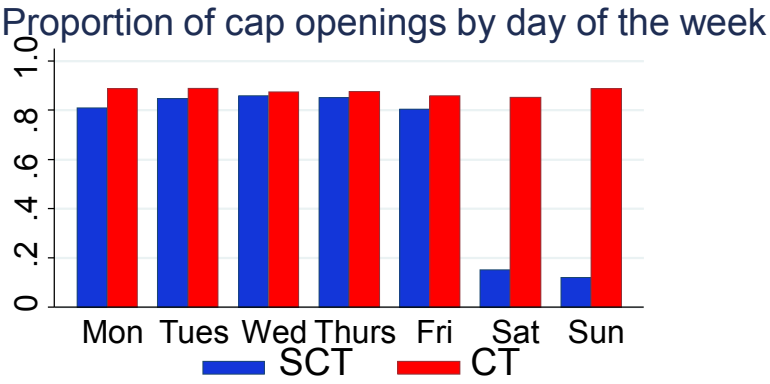
Adherence questionnaires: YP claimed to take >95% of scheduled drugs.
No significant differences between arms.

Mean % days on ART: 72.8% for SCT vs 99.8% for CT.

MEMs cap substudy:

Enrolled: 61 YP: (31 SCT, 30 CT)
At 48 wks: 46 YP: (23 SCT, 23 CT)

Median (IQR) cap openings/week
5 (4,5) SCT vs **7** (6,7) CT.



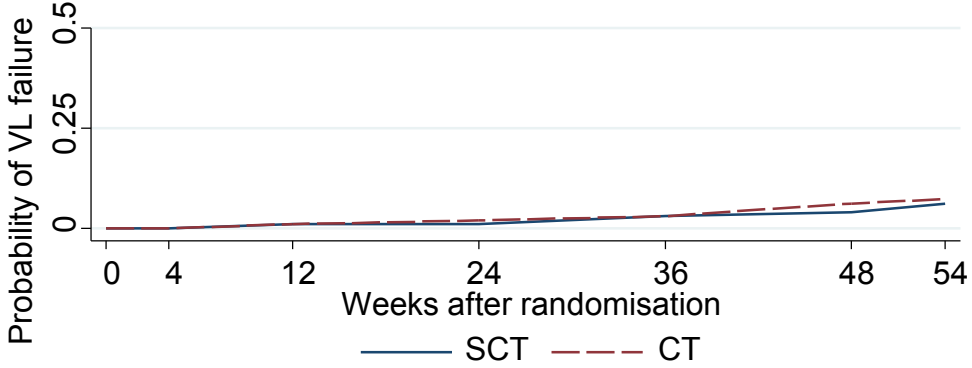
MCV levels (among patients on zidovudine):

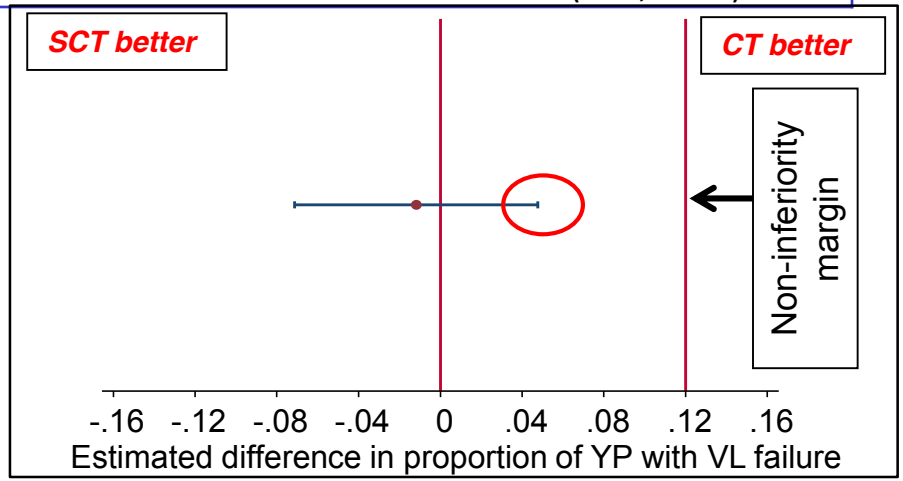
MCV significantly lower in SCT vs CT at every visit week
suggesting less exposure to ZDV compared to those in the CT arm.

Primary Endpoint: VL ≥50c/ml (confirmed)

Week 48 assessment				
	Number of events	Person years at risk	Estimated probability of failing*	(90% CI)
SCT	6	99.5	6.1%	(2.1, 10.2%)
CT	7	98.8	7.3%	(2.9, 11.7%)
Difference (SCT-CT)			-1.2%	(-7.3, 4.9%)

Kaplan-Meier graph adjusted for age and region





Upper bound of difference between survival curves= 4.9%, which lies well inside the non-inferiority margin of 12%

Results are consistent with non-inferiority of SCT compared to CT

Secondary Endpoints: Resistance

HIV-1 MAJOR RESISTANCE MUTATIONS	SCT n/N	CT n/N
Sequence available/Virologic Failure	3/6	6/7
Resistance: Any Class	2/3	5/6
NNRTI	1/3	4/6
NNRTI & NRTI (M184)	1/3	1/6

All 4 YP who failed without sequence data **re-suppressed** after reaching the primary endpoint, indicating resistance unlikely

Secondary Endpoints & Biomarker Substudy

- No significant differences in CD4 or CD8 count or percent
- Overall no difference in lipid profiles
  - Transient increase in LDL cholesterol in SCT at 24 weeks only
- Platelet counts lower in SCT arm at each follow up visit ($p<0.05$)

- **Biomarker substudy:** There were no differences between arms in 19 biomarkers of inflammation
  - Only borderline difference in D-Dimers in favour SCT ($p=0.048$)

Changes in ARV Regimen and in Strategy

Regimen Change: 4 changes in SCT arm, compared to 11 in CT arm (p=0.105)

	SCT		CT		Total	
Number still on initial regimen at 48 week assessment: n (%)	95	(96.0)	88	(88.9)	183	(92.0)
Change in ART regimen	4	(4.0)	11	(11.1)	13	(6.6)
Unknown – Lost to follow up	0		1		1	
Reasons for ART regimen change:						
Toxicity	2		6		8	
Simplification	1		3		4	
Compliance	1		1		2	
VL failure	0		1		1	

8 Changed Strategy (5 ➔7 day ART a week):

- 6 due to reaching the primary endpoint
- 1 due to an AE leading to discontinuation in EFV (gynaecomastia)
- 1, although remaining suppressed, changed from SCT to CT because poor adherence was noted

Safety

No deaths or CDC stage C events

	SCT		CT		Total		
	episodes	(YP)	episodes	(YP)	episodes	(YP)	p value*
Grade 3 and 4 AEs	14	(8)	17	(12)	31	(20)	0.480
ART related AEs	2	(2)	16	(8)	18	(10)	0.101
Treatment modifying AEs	1	(1)	1	(1)	2	(2)	1.000
SAEs	7	(6)	6	(3)	13	(9)	0.331

*Fisher's exact test

- No significant differences in terms of number of young people with adverse events
- Some evidence of more ART related AEs in the CT arm than the SCT arm
- The only SAE reported more than once was spontaneous abortion (1 SCT, 1CT)
- Additionally, there were 5 pregnancies (1 SCT, 4 CT)

Acceptability (answered only by SCT arm)

Comparison of things people found difficult before vs. during the study.

	Baseline	End of study	p value
Remembering to take meds	21	16	0.424
Timing of meds	18	14	0.503
Number of tablets	8	5	0.549
Size of tablets	9	5	0.388
Difficulty swallowing	9	3	0.146
Amount of syrup	1	1	1.000
Taste of meds	12	7	0.227
Side effects	10	5	0.302
Different routine (weekends)	8	2	0.109
Different routine (week days)	4	2	0.688
School/college days	5	1	0.125
School/college holidays	6	4	0.754
Staying with friends/family	12	17	0.332
Going out with friends	15	2	0.001
Other	11	5	0.210

74% young people said SCT made things a lot easier and 16% said a little easier (63% and 16% at baseline)

What did Young People Say?
Breather Social Science SubStudy

- Liked strategy
- Social life better
- Side effects less at week ends
  - these often not previously disclosed
- Time to adjust
- May not be suitable for all

Bernays S, et al personal communication

BREATHER: Conclusions

- 94% of all YP remained virally suppressed, <50c/ml, to 48 weeks (97% <400c/ml)
- Over 48 weeks for SCT vs CT
  - 1% difference in viral suppression in favour of SCT
  - Primary and alternate analyses consistent
- No evidence of major difference in toxicity parameters
  - Except more reported ART related toxicity in CT
- No difference in clinical, immunologic or virological parameters, or in inflammatory biomarkers or major resistance mutations
- 27% reduction in drug exposure
- Acceptability questionnaires favourable towards SCT
- Long term follow up for 2 additional years has commenced

Non-inferiority of VL suppression in young people on EFV-based first line ART was demonstrated for SCT vs CT

Acknowledgements

This trial was sponsored by the Paediatric European Network for Treatment of AIDS (PENTA) Foundation.

Funding for this study was provided by the European Union Seventh Framework Programme (FP7/2007-2013) under EuroCoord grant agreement nº 260694 with support for trial management and clinical sites in the UK and Ireland from the National Institute for Health Research's HTA Programme

We thank all of the young people, their families, and staff from the centres participating in the BREATHER trial

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L= Laboratory, P = Pharmacy, S = Social Scientist

Thank You

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