

1 SUMMARY

1.1 Aim and Objectives

The overall aim of the PENTA 16 trial is to evaluate the role of Short-Cycle Therapy (SCT) in the management of HIV-infected young people who have responded well to antiretroviral therapy (ART) and to determine whether young people with chronic HIV infection undergoing Short-Cycle Therapy of five days on ART and two days off maintain the same level of viral load suppression as those on continuous therapy, over 48 weeks.

To assess the advantages and disadvantages of the strategy, the incidence of toxicities, immunological control, resistance mutations, acceptability, quality of life and adherence to the randomised strategy will also be compared.

Importantly, because of insufficient data on short-term viral load rebound after stopping ART in this population, the trial will incorporate an initial pilot phase in selected centres, to assess the safety of the SCT strategy by evaluating detailed HIV-1 RNA profiles of participants on the SCT strategy.

For an overview of the trial design please see schematic diagram 1.8.

1.2 Design

PENTA 16 is an open, randomised, parallel group phase II/III trial. Young people will be randomised 1:1 into two groups:

1. Continuous ART
2. Short-Cycle Therapy

Young people randomised to SCT will follow a cycle of 5 days on ART (Monday-Friday or Sunday-Thursday) and 2 days off (Saturday-Sunday or Friday-Saturday). Participants may choose which 2 days off ART they would prefer and whichever are chosen must be continued throughout the entire time on SCT within the study.

The first 15 participants enrolled in the SCT arm of the study will be included in the pilot phase and will have weekly HIV-1 RNA measurements during the first 3 weeks of the study. Recruitment to the continuous arm will run concurrently. The IDMC will meet at the end of the pilot phase to review the data collected. Recruitment will be on hold at other centres until this meeting has taken place.

1.3 Population

160 HIV-1 infected young people, male and female, aged 8 to 21 years on a stable first-line HAART regimen containing at least 2 NRTIs and EFV for at least 12 months and willing to continue the regimen throughout the study period. Young people on regimens containing NVP or a boosted protease inhibitor with undetectable viral load wishing to enrol should switch to EFV, and may be enrolled if they have 3 subsequent HIV-1 RNA measurements <50 copies/ml over a minimum period of 12 weeks.

Young people will be recruited from clinical centres in countries participating in the PENTA and PHPT (Thailand) networks.

1.4 Outcome measures

Primary Outcome:

- HIV-1 RNA ≥ 50 c/ml (confirmed on a separate sample within 1 week) at any of week 4, 8, 12, 24, 36 or 48.

Secondary Outcomes:

- HIV-1 RNA < 50 c/ml at 24 and 48 weeks.
- number of HIV mutations present at week 4, 8, 12, 24, 36 or 48 conferring resistance to drugs taken at randomisation or during the trial.
- change in CD4 (absolute and percentage) from randomisation to 24 and 48 weeks.
- change in ART (defined as any change from the ART regimen at randomisation).
- ART-related grade 3 or 4 clinical and laboratory adverse events.
- new CDC stage C diagnosis or death
- changes in fasting cholesterol, triglycerides, LDL, HDL and VLDL levels through 48 weeks.
- adherence, acceptability, and quality of life over 48 weeks as assessed by patient completed questionnaires.

1.5 Follow-up

All young people will be seen for clinic visits at weeks -4 to -2 (screening), 0 (randomisation), 4, 8, 12, 24, 36 and 48. Young people in the SCT arm will also be seen for phlebotomy visits (HIV-1 RNA and blood store only) at week 1. Young people in the SCT arm in the pilot phase will have 2 additional phlebotomy visits (HIV-1 RNA measured only) at weeks 2 and 3.

The clinician may request more frequent visits for young people in either arm, if required. The flowcharts (sections 1.9, 1.10, 1.11) indicate the minimum number of visits for protocol completion and data recording. However it is the investigator's responsibility to see participants as frequently as necessary, particularly for the monitoring of adverse events.

All participants with a HIV-1 RNA measurement ≥ 50 c/ml will be brought in for a confirmatory viral load measurement on a separate sample within 1 week. For those on the SCT arm, there should not be any further interruptions to antiretroviral therapy until the repeat test result is obtained.

Participants in the SCT arm with a viral rebound of ≥ 50 c/ml that is confirmed on repeat testing will be placed back on continuous ART and should not undergo further interruptions to their therapy.

Participants in the SCT arm with a viral load measurement of $\geq 10,000$ c/ml should be put back on to continuous ART immediately without waiting for a confirmatory viral load.

Participants in the SCT arm with an isolated "blip" of HIV-1 RNA ≥ 50 c/ml and $< 10,000$ c/ml with subsequent measurement < 50 c/ml will remain on SCT.

There can only be a maximum of 3 blips within the study. After the third blip, continuous ART should be resumed with no further interruptions.

Participants on continuous ART with a confirmed viral load ≥ 50 c/ml, should receive standard clinical care.

1.6 Duration

Young people will be recruited over 18 months and followed until the last randomised participant has completed 48 weeks of follow-up. Participants being followed after week 48 should be seen every 12 weeks, until the last young person has completed follow-up. Participants randomised to the SCT arm should continue to follow the SCT strategy unless the clinician or the family have concerns which they should discuss with the appropriate Trials Unit.

1.7 Substudies

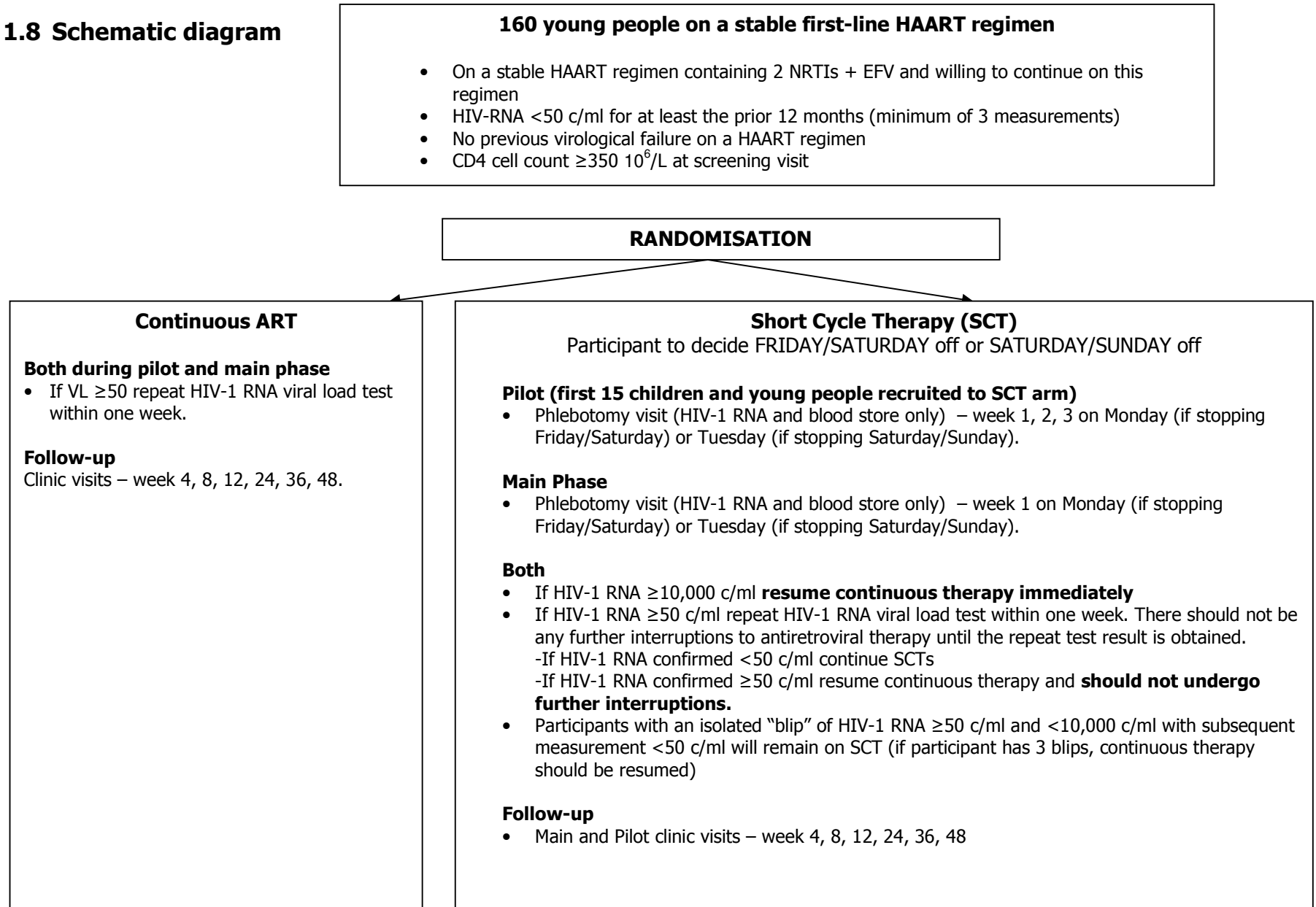
1.7.1 Virology/Immunology Substudy (Appendix 11)

Plasma and cell storage will be required in both arms throughout the trial for detailed virological and immunological assessments (see Appendix 11). Flowsheets in section 1.9, 1.10 and 1.11 give details of the timing of plasma and cell storage.

1.7.2 Qualitative Substudy – UK and Ireland only (Appendix 12)

The qualitative substudy, will be co-ordinated by London School of Hygiene and Tropical Medicine will involve interviews and audio diaries in a subset of 20 participants (at least 10 in the SCT arm) to gain information on a young person's experiences and feelings towards identity, treatment experience, adherence, transition to adulthood, expectation, and trial experience at the beginning and end of the study. Focus groups maybe conducted if feasible at the end of the study.

1.8 Schematic diagram



1.9 FLOWSHEET FOR SCT PARTICIPANTS IN PILOT PHASE OF STUDY (first 15 randomisations to SCT)

WEEK	Screening -4 to -2	Randomisation 0	1, 2, 3 (Mon/Tues)	4	8	12	24	36	48	Further follow-up	End of study visit
SCT arm											
Signed informed consent	X	(confirm)									
Clinical assessment ^a	X	X		X	X	X	X	X	X	Every 12 weeks	X
Tanner scales	X						X		X	Every 24 weeks	X
Lipodystrophy assessment	X						X		X	Every 48 weeks	X
Local HIV-1 RNA viral load	X	X	X	X	X	X	X	X	X	Every 12 weeks	X
T cell lymphocyte subsets inc. RO/RA phenotype	X	X		X	X	X	X	X	X	Every 12 weeks	X
Biochemistry ^b	X	X				X	X	X	X	Every 12 weeks	X
Haematology ^c	X	X				X	X	X	X	Every 12 weeks	X
Lipids/glucose ^d		X					X		X	Every 24 weeks	X
Pregnancy Test ^e	X						X		X	Every 24 weeks	X
Plasma storage ^f	X	X	X	X	X	X	X	X	X	Every 12 weeks	X
Cell storage ^f	X	X	X	X	X	X	X	X	X	Every 24 weeks	X
Adherence questionnaire	X			X		X	X	X	X	Every 12 weeks	X
Acceptability Questionnaire		X								If re-start continuous ART	X
PedsQL™ Questionnaire		X					X		X	Every 24 weeks	X

Note: shaded boxes indicate visits where overnight fasting is required for blood lipids/glucose. *If insufficient blood is drawn, priorities are: local HIV-1 RNA, T cell subsets, plasma store, lipids/glucose, biochemistry, haematology*

(a) Clinical assessment: including height & weight (adjust doses), presence of adverse events and change in HIV disease stage (including clinical lipodystrophy).

(b) Biochemistry: Creatinine, Bilirubin, ALT, AST, Alkaline Phosphatase, Albumin

(c) Haematology: Hb, MCV, WBC, Lymphocytes, Neutrophils, Platelets

(d) Lipids/Glucose: Triglycerides, Cholesterol (Total, HDL, LDL, VLDL), Glucose. Overnight fasting required at randomisation and weeks 24 and 48, and at other times if possible

(e) Pregnancy Test: either a urine sample. This test will be performed for all females of childbearing potential at screening, and weeks 24 and 48 (then every 24 weeks) and at other time-points if required. The initial pregnancy test must be done within 72 hours of enrolment and its results must be received before randomisation.

(f) 16ml total blood draw for plasma and cell storage: 6.0ml in EDTA for separation and storage of plasma at -80°C (see Manual of Operations for instructions for plasma handling and storage), 10ml of whole blood for cell storage (if not doing cell storage, just take 6ml)

1.10 FLOWSHEET FOR MAIN PHASE OF STUDY: SCT arm (after pilot fully recruited)

WEEK	Screening -4 to -2	Randomisation 0	1 (Mon/Tues)	4	8	12	24	36	48	Further follow-up	End of study visit
SCT arm											
Signed informed consent	X	(confirm)									
Clinical assessment ^a	X	X		X	X	X	X	X	X	Every 12 weeks	X
Tanner scales	X						X		X	Every 24 weeks	X
Lipodystrophy assessment	X						X		X	Every 48 weeks	X
Local HIV-1 RNA viral load	X	X	X	X	X	X	X	X	X	Every 12 weeks	X
T cell lymphocyte subsets inc. RO/RA phenotype	X	X		X	X	X	X	X	X	Every 12 weeks	X
Biochemistry ^b	X	X				X	X	X	X	Every 12 weeks	X
Haematology ^c	X	X				X	X	X	X	Every 12 weeks	X
Lipids/glucose ^d		X					X		X	Every 24 weeks	X
Pregnancy Test ^e	X						X		X	Every 24 weeks	X
Plasma storage ^f	X	X	X	X	X	X	X	X	X	Every 12 weeks	X
Cell storage ^f	X	X	X	X	X	X	X	X	X	Every 24 weeks	X
Adherence questionnaire	X			X		X	X	X	X	Every 12 weeks	X
Acceptability Questionnaire		X								If re-start continuous ART	X
PedsQL™ Questionnaire		X					X		X	Every 24 weeks	X

Note: shaded boxes indicate visits where overnight fasting is required for blood lipids/glucose. *If insufficient blood is drawn, priorities are: local HIV-1 RNA, T cell subsets, plasma store, lipids/glucose, biochemistry, haematology*

(a) Clinical assessment: including height & weight (adjust doses), presence of adverse events and change in HIV disease stage (including clinical lipodystrophy).

(b) Biochemistry: Creatinine, Bilirubin, ALT, AST, Alkaline Phosphatase, Albumin

(c) Haematology: Hb, MCV, WBC, Lymphocytes, Neutrophils, Platelets

(d) Lipids/Glucose: Triglycerides, Cholesterol (Total, HDL, LDL, VLDL), Glucose. Overnight fasting required at randomisation and weeks 24 and 48, and at other times if possible

(e) Pregnancy Test: either a urine sample. This test will be performed for all females of childbearing potential at screening, and weeks 24 and 48 (then every 24 weeks) and at other time-points if required. The initial pregnancy test must be done within 72 hours of enrolment and its results must be received before randomisation.

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1.11 FLOWSHEET FOR MAIN PHASE OF STUDY: CONTINUOUS ART ARM (and those in SCT arm who resume continuous ART)

WEEK	Screening -4 to -2	Randomisation 0	4	8	12	24	36	48	Further follow-up	End of study visit
Continuous ART arm										
Signed informed consent	X	(confirm)								
Clinical assessment ^a	X	X	X	X	X	X	X	X	Every 12 weeks	X
Tanner scales	X					X		X	Every 24 weeks	X
Lipodystrophy assessment	X					X		X	Every 48 weeks	X
Local HIV-1 RNA viral load	X	X	X	X	X	X	X	X	Every 12 weeks	X
T cell lymphocyte subsets inc. RO/RA phenotype	X	X	X	X	X	X	X	X	Every 12 weeks	X
Biochemistry ^b	X	X			X	X	X	X	Every 12 weeks	X
Haematology ^c	X	X			X	X	X	X	Every 12 weeks	X
Lipids/glucose ^d		X				X		X	Every 24 weeks	X
Pregnancy Test ^e	X					X		X	Every 24 weeks	X
Plasma storage ^f	X	X	X	X	X	X	X	X	Every 12 weeks	X
Cell storage ^f	X	X	X	X	X	X	X	X	Every 24 weeks	X
Adherence questionnaire	X		X		X	X	X	X	Every 12 weeks	X
Acceptability Questionnaire									If in SCT arm & re-start continuous ART	If in SCT arm & re-starting continuous ART
PedsQL™ Questionnaire		X				X		X	Every 24 weeks	X

Note: shaded boxes indicate visits where overnight fasting is required for blood lipids/glucose. *If insufficient blood is drawn, priorities are: local HIV-1 RNA, T cell subsets, plasma store, lipids/glucose, biochemistry, haematology*

(a) Clinical assessment: including height & weight (adjust doses), presence of adverse events and change in HIV disease stage (including clinical lipodystrophy).

(b) Biochemistry: Creatinine, Bilirubin, ALT, AST, Alkaline Phosphatase, Albumin

(c) Haematology: Hb, MCV, WBC, Lymphocytes, Neutrophils, Platelets

(d) Lipids/Glucose: Triglycerides, Cholesterol (Total, HDL, LDL, VLDL), Glucose. Overnight fasting required at randomisation and weeks 24 and 48, and at other times if possible

(e) Pregnancy Test: either a urine sample. This test will be performed for all females of childbearing potential at screening, and weeks 24 and 48 (then every 24 weeks) and at other time-points if required. The initial pregnancy test must be done within 72 hours of enrolment and its results must be received before randomisation.

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