

# Paediatric European Network for Treatment of AIDS



## BREATHER

### (PENTA 16) Trial Summary

Short-Cycle Therapy (SCT) (5 days on/2 days off) in young people with chronic HIV-infection

#### 1.1 Aim and Objectives

The overall aim of the BREATHER 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

BREATHER 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

### Pilot Phase

The first participants randomised in the study (15 in the SCT arm) will be included in the pilot phase and will have weekly HIV-1 RNA measurements during the first 3 weeks of the study. Those randomised to the SCT arm and included in the pilot phase should stop taking their antiretrovirals on Saturdays and Sundays i.e. will follow a cycle of 5 days on ART (Monday-Friday) and 2 days off (Saturday-Sunday) during the pilot phase. Recruitment to the continuous arm will run concurrently; young people randomised to continuous ART will continue their current ART regimen.\* The IDMC will meet at the end of the pilot phase to review interim data. Recruitment will be on hold until this review has taken place.

### Main Trial

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 randomised to the SCT arm and included in this phase of the trial 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. Young people randomised to continuous ART will continue their current ART regimen\*.

\*Young people randomised to continuous ART should only stop or switch all drugs in their ART regimen for virological, immunological or clinical failure according to local practice. However if simplification of the ART regimen or substitution of one drug is deemed necessary for clinical reasons, this may be allowed after discussion with the appropriate Trials Unit.

## 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, that have an undetectable viral load for at least 12 months and are willing to continue the regimen throughout the study period. Young people on regimens containing NVP or a boosted protease inhibitor with undetectable viral load for at least 12 months wishing to enrol should first switch to EFV, and may be enrolled if they have 2 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; PHPT and HIV-NAT networks (Thailand); and a single centre in Uganda.

## 1.4 Outcome measures

### Pilot Phase Outcome Measure:

HIV-1 RNA  $\geq 50$  copies/ml, reproduced on a repeat test of the same sample off ART on the Monday following SCT at any of week 1, 2, 3 (see section 11.5).

### Primary Outcome:

- HIV-1 RNA  $\geq 50$  copies/ml (**confirmed** on a separate sample within 1 week) at any of week 4, 12, 24, 36 or 48.

### **Secondary Outcomes:**

- HIV-1 RNA  $< 50$  copies/ml at 24 and 48 weeks.
- Number of HIV mutations present at week 4, 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).
- Grade 3 or 4 clinical and laboratory adverse events.
- ART treatment modifying adverse events (all grades).
- New CDC stage B or C diagnosis or death
- Changes in fasting glucose, 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 (pilot only), 12, 24, 36 and 48.

Young people in the pilot phase will have 3 additional phlebotomy visits (HIV-1 RNA and blood store only) at weeks 1, 2, 3 and 8. For young people in the SCT arm these blood draws will be on the Monday after the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> weekends off ART respectively and before ART recommences; for young people in the continuous arm these blood draws can be at any time during the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> weeks.

The clinician may request more frequent visits for young people in either arm, if required. The flowcharts (sections 1.9, 1.10, 1.11, 1.12) 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.

### **Management of young people and viral load tests (see Flow diagram)**

#### **Pilot Phase**

Current PCR tests for HIV-1 RNA can occasionally yield spurious results suggestive of low level viremia. During the pilot phase only, any HIV-1 RNA measurement that is detected at  $\geq 50$  c/ml at weeks 1, 2 or 3 will be repeated on the SAME SAMPLE to ensure that the result is valid and reproducible.

#### **SCT arm:**

Any participant with a reproducible viral load of  $> 50$  c/ml (2 tests on the SAME sample) after the first weekend off treatment will not have a break over the 2<sup>nd</sup> weekend. On the Monday visit on week 2 after having taken medications at the weekend, the viral load will be repeated (confirmatory test).

- If this result is  $\geq 50$  c/ml then the participant should not undertake any further interruptions.
- If the confirmed test is  $< 50$  c/ml, then the young person may undergo an interruption over the third weekend. If the young person has a 2<sup>nd</sup> reproducible viral load  $> 50$  c/ml (2 tests on the SAME sample) after the third weekend, the young person should not undertake any further interruptions.

**CT arm:**

Participants with a reproducible viral load  $\geq 50$  c/ml (2 tests on the SAME sample), should receive standard clinical care.

**Main Trial**

**SCT arm:**

Participants with a HIV-1 RNA measurement  $\geq 50$  c/ml will have a confirmatory viral load measurement on a SEPARATE SAMPLE within 1 week. No further interruptions to antiretroviral therapy should be undertaken until the repeat test result is obtained.

Participants with a confirmed viral rebound of  $\geq 50$  c/ml should re-commence continuous ART and should not undergo further interruptions to their therapy.

Participants with an isolated increase of HIV-1 RNA  $\geq 50$  c/ml and subsequent measurement  $< 50$  c/ml can remain on SCT. There can only be a maximum of 3 such occurrences during the lifetime of the study. After the third increase, continuous ART should be resumed with no further interruptions.

**CT arm:**

Participants with a HIV-1 RNA measurement  $\geq 50$  c/ml will have a confirmatory viral load measurement on a SEPARATE SAMPLE within 1 week. Participants with a confirmed viral load  $\geq 50$  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 the clinician should discuss with the appropriate Trials Unit.

## **1.7 Substudies**

### **1.7.1 Virology/Immunology Substudy**

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, 1.11 and 1.12 give details of the timing of plasma and cell storage.

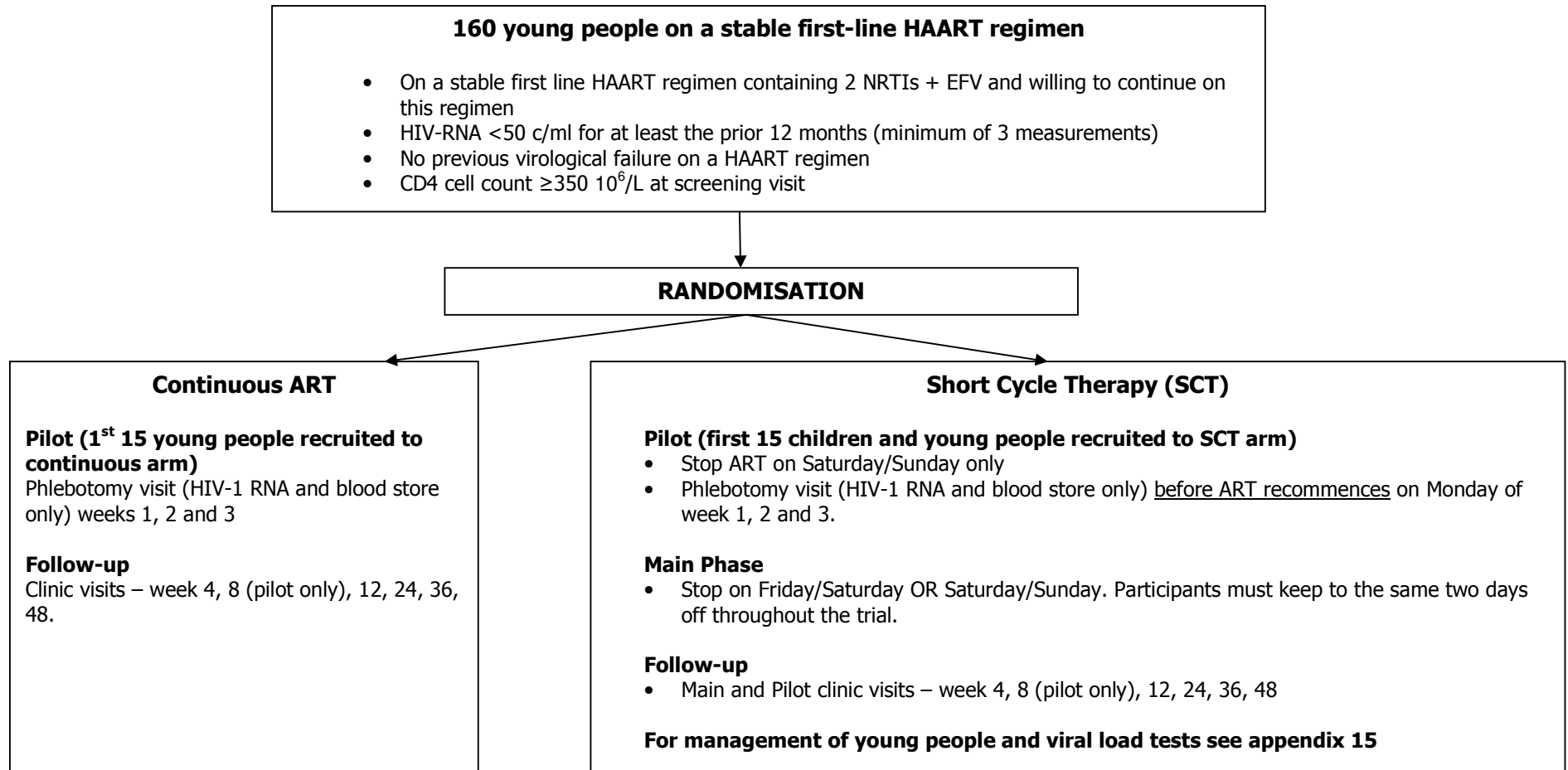
### **1.7.2 Qualitative Substudy – UK, Ireland and Uganda only**

The qualitative substudy, will be co-ordinated by London School of Hygiene and Tropical Medicine. This will involve interviews and audio diaries in a subset of 40 participants (20 in UK and Ireland, 20 in Uganda with a total of at least 20 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 may be conducted if feasible at the end of the study.

### **1.7.3 Adherence (MEMS cap) substudy – UK, Thailand (HIV-NAT) and Uganda only**

The adherence substudy will be carried out in a subset of 60 participants from the UK, Thailand (HIV-NAT) and Uganda (30 SCT, 30 continuous treatment). Additional consent will be sought for enrolment into this substudy which will use Medication Event Monitoring Systems [MEMS]; Apex Corporation, Menlo Park, California to measure adherence to the protocol for both arms of the trial. MEMS caps fit standard size medication bottles, and record the time and date of each opening as a presumptive dose. MEMS cap electronic monitors will be used on one of the antiretroviral medication taken the most frequently for two 12-week periods in each participant.

## 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) <sup>f</sup>	4	8	12	24	36	48	Further follow-up	End of study visit
<b>SCT arm</b>											
Signed informed consent	X	(confirm)									
Clinical assessment <sup>a</sup>	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 <sup>g</sup>	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 <sup>b</sup>	X	X				(X)	(X)	(X)	X	As per local practise	X
Haematology <sup>c</sup>	X	X				X	X	X	X	Every 12 weeks	X
Lipids/glucose <sup>d</sup>		X					X		X	Every 48 weeks	X
Pregnancy Test <sup>e</sup>	X						X		X	Every 24 weeks	X
Plasma storage <sup>g</sup>	X	X	X	X	X	X	X	X	X	Every 12 weeks	X
Cell storage <sup>g</sup>	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

Notes: shaded boxes indicate visits where overnight fasting is required for blood lipids/glucose.

(X) – Indicates optional investigations.

*If insufficient blood is drawn, priorities are: local HIV-1 RNA, T cell subsets, plasma store, lipids/glucose, biochemistry, and 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 and Albumin. Calcium and Phosphate at baseline and annually thereafter.

(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 then every 48 weeks.

(e) Pregnancy Test: either a blood or 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) Weeks 1,2,3 phlebotomy visits should be before recommencing ART on the Monday; sufficient blood should be sent to the virology laboratory for a repeat measurement of the same sample.

(g) 16ml total blood draw in EDTA for plasma and cell storage: 6.0ml in EDTA if plasma store only (see Manual of Operations for instructions for plasma and cell handling and storage).

## 1.10 FLOWSHEET FOR CT PARTICIPANTS IN PILOT PHASE OF STUDY (first 15 randomisations to continuous arm).

WEEK	Screening -4 to -2	Randomisation 0	1, 2, 3 f	4	8	12	24	36	48	Further follow-up	End of study visit
<b>SCT arm</b>											
Signed informed consent	X	(confirm)									
Clinical assessment <sup>a</sup>	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 <sup>g</sup>	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 <sup>b</sup>	X	X				(X)	(X)	(X)	X	As per local practise	X
Haematology <sup>c</sup>	X	X				X	X	X	X	Every 12 weeks	X
Lipids/glucose <sup>d</sup>		X					X		X	Every 48 weeks	X
Pregnancy Test <sup>e</sup>	X						X		X	Every 24 weeks	X
Plasma storage <sup>g</sup>	X	X	X	X	X	X	X	X	X	Every 12 weeks	X
Cell storage <sup>g</sup>	X	X		X		X	X		X	Every 24 weeks	X
Adherence questionnaire	X			X		X	X	X	X	Every 12 weeks	X
PedsQL™ Questionnaire		X					X		X	Every 24 weeks	X

Notes: shaded boxes indicate visits where overnight fasting is required for blood lipids/glucose.

(X) – Indicates optional investigations.

*If insufficient blood is drawn, priorities are: local HIV-1 RNA, T cell subsets, plasma store, lipids/glucose, biochemistry, and 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 and Albumin. Calcium and Phosphate at baseline and annually thereafter.

(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 then every 48 weeks.

(e) Pregnancy Test: either a blood or 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) Weeks 1,2,3 phlebotomy visits at any time during the week; sufficient blood should be sent to the virology laboratory for a repeat measurement of the same sample.

(g) 16ml total blood draw in EDTA for plasma and cell storage: 6.0ml in EDTA if plasma store only (see Manual of Operations for instructions for plasma and cell handling and storage).

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

WEEK	Screening -4 to -2	Randomisation 0	4	12	24	36	48	Further follow-up	End of study visit
<b>SCT arm</b>									
Signed informed consent	X	(confirm)							
Clinical assessment <sup>a</sup>	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	Every 12 weeks	X
T cell lymphocyte subsets inc. RO/RA phenotype	X	X	X	X	X	X	X	Every 12 weeks	X
Biochemistry <sup>b</sup>	X	X		(X)	(X)	(X)	X	As per local practise	X
Haematology <sup>c</sup>	X	X		X	X	X	X	Every 12 weeks	X
Lipids/glucose <sup>d</sup>		X			X		X	Every 48 weeks	X
Pregnancy Test <sup>e</sup>	X				X		X	Every 24 weeks	X
Plasma storage <sup>f</sup>	X	X	X	X	X	X	X	Every 12 weeks	X
Cell storage <sup>f</sup>	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

Notes: shaded boxes indicate visits where overnight fasting is required for blood lipids/glucose.

(X) – Indicates optional investigations.

*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 and Albumin. Calcium and Phosphate at baseline and annually thereafter.

(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 then every 48 weeks.

(e) Pregnancy Test: either a blood or 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 if plasma store only. [see Manual of Operations for instructions for plasma and cell handling and storage].

## 1.12 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	12	24	36	48	Further follow-up	End of study visit
<b>Continuous ART arm</b>									
Signed informed consent	X	(confirm)							
Clinical assessment <sup>a</sup>	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	Every 12 weeks	X
T cell lymphocyte subsets inc. RO/RA phenotype	X	X	X	X	X	X	X	Every 12 weeks	X
Biochemistry <sup>b</sup>	X	X		(X)	(X)	(X)	X	As per local practise	X
Haematology <sup>c</sup>	X	X		X	X	X	X	Every 12 weeks	X
Lipids/glucose <sup>d</sup>		X			X		X	Every 48 weeks	X
Pregnancy Test <sup>e</sup>	X				X		X	Every 24 weeks	X
Plasma storage <sup>f</sup>	X	X	X	X	X	X	X	Every 12 weeks	X
Cell storage <sup>f</sup>	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

Notes: shaded boxes indicate visits where overnight fasting is required for blood lipids/glucose.

(X) – Indicates optional investigations.

*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 and Albumin. Calcium and Phosphate at baseline and annually thereafter.

(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 then every 48 weeks.

(e) Pregnancy Test: either a blood or 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.

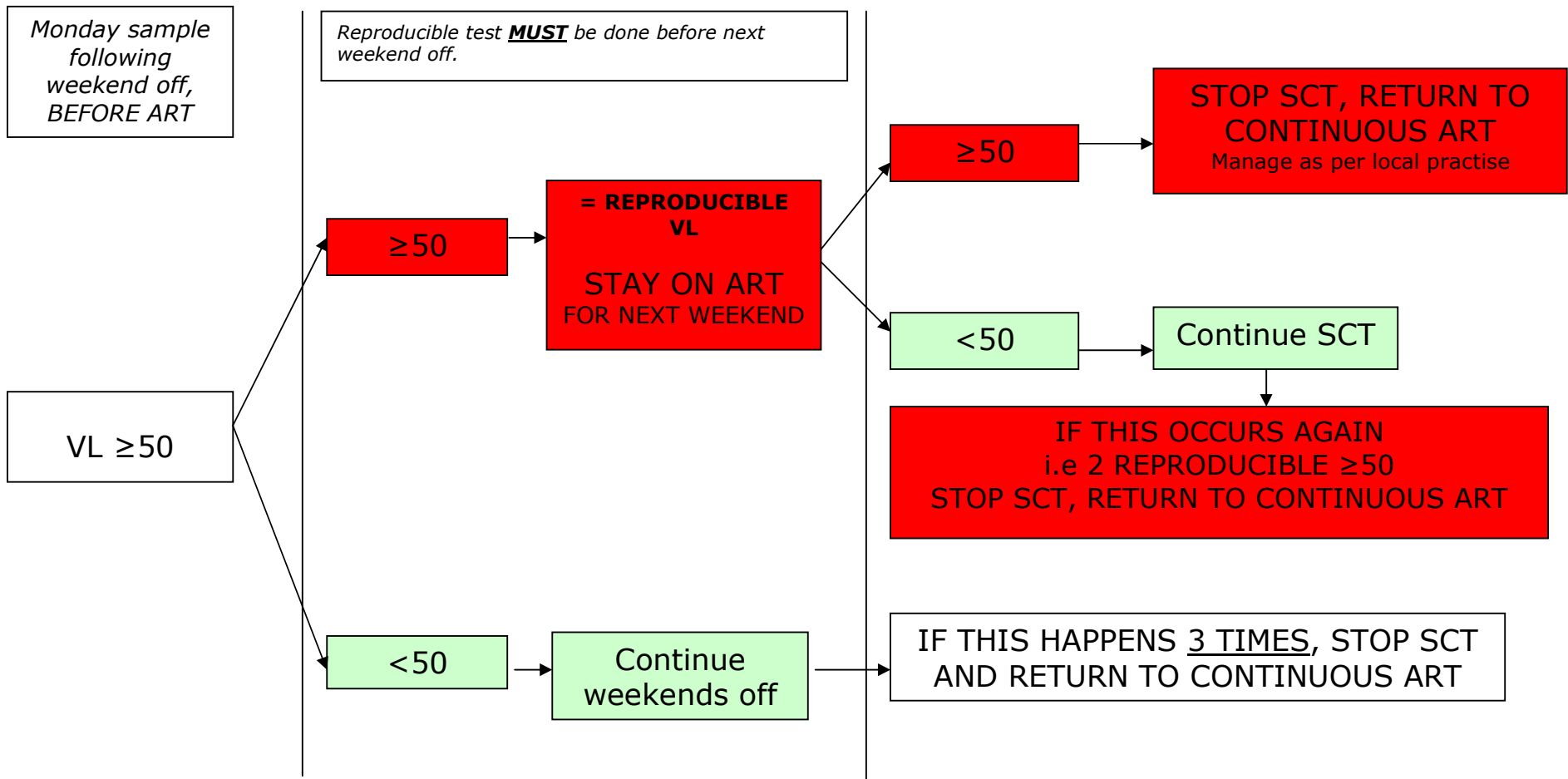
(f) 16ml total blood draw for plasma and cell storage: 6.0ml in EDTA if plasma store only [see Manual of Operations for instructions for plasma and cell handling and storage].

# FLOW CHART FOR MANAGING VIRAL LOADS (SCT GROUP ONLY)

## PILOT PHASE

**ANY VL**

**REPEAT on SAME SAMPLE (Reproducible) Following week**



## **MAIN TRIAL**

