

Development of AntiRetroviral Therapy in Africa

ACRONYM: DART

Full Title of trial:

A randomised trial of monitoring practice and structured treatment interruptions in the management of antiretroviral therapy in adults with HIV infection in Africa

ISRCTN: 13968779

Protocol number 1.2

Protocol date 24 August 2004

.....
Authorised signature

.....
Date

(Chair of TSC for final protocols and amended final protocols)

SUBSTANTIVE CHANGES FROM DART PROTOCOL V1.1 TO V1.2 (important changes in bold)

- Change of various contact details.
- **Amendment of CD4 threshold for STI randomisation to 300 cells/mm³, throughout.**
- **Amendment of time for STI randomisation to week 52 (using week 48 CD4 count for eligibility), throughout.**
- **Amendment of recruitment target for STI/CT randomisation to 600, throughout.**
- **Recruitment target revised to 3300, throughout.**
- **Recruitment period for CMO/LCM extended into 2nd year, throughout.**
- **Recruitment period for STI/CT extended into 3rd year, throughout.**
- Trial schema revised, section 1.2, page 12.
- **Flow sheets revised for STI changes, section 1.3, page 13.**
- **Flow sheets revised to make 12 weekly plasma storage mandatory and addition of plasma storage at (or near) time of delivery, section 1.3, page 13.**
- NORA will not take place in Zimbabwe, throughout.
- **Addition of specific eligibility criteria for STI randomisation, section 7.3.3, page 26.**
- **Addition of intensive monitoring of first 100 patients randomised to STI/CT, section 7.3.3, page 26.**
- **Revision of criteria for restarting ART early during an STI, section 7.5.2, page 29.**
- **Revision of criteria and procedure for deferring an STI, section 7.5.3, page 29.**
- **Revision of CD4 threshold and time on ART for resuming STIs after switch to second line, removal of recurrent bacterial infection for clinical reason for switching and reduction of time for repeating CD4 counts if <50, section 7.6.2, page 30.**
- **Updating of sample size calculations, section 10.1, page 36.**

SUBSTANTIVE CHANGES FROM DART PROTOCOL V1.0 TO V1.1 (important changes in bold)

- Change of PI details at MRC/UVRI Entebbe.
- Addition of contact details for Project Leader at MRC/UVRI Entebbe.
- Addition of Investigators at Harare and Academic Alliance.

- Update of various contact details.
- Addition of details of trial managers at sites and at CTU.
- **Section 4.2: addition of 2 extra secondary endpoints.**
- Section 5.1.2: CD4 monitoring should not be open for CMO patients in the STI pilot
- **Section 6.2 point 5: replacement of WBC as example exclusion criterion with neutrophils $<0.50 \times 10^9/l$.**
- **Section 6.3: inclusion of Harare site in the NORA substudy.**
- Section 7.1: removal of cell percentages from required cell counts.
- Section 7.3.1: CMO/LCM stratification corrected to 0-99 and 100-199 CD4 not 1-99 and 100-200.
- Section 7.3.1: STI/CT stratification by week number at entry.
- Section 7.3.3: remove requirement to fax CTU.
- Section 7.3.3: extend period on other ARVs from 5 to 7 days on stopping NVP.
- Section 7.3.5: clarification about families and NORA.
- **Section 7.4: change to reporting of grade 4 biochemistry in CMO arm.**
- Section 7.5.1: extend period on other ARVs from 5 to 7 days on stopping NVP.
- Section 7.6.2: allowance for some clinical discretion about reasons for switching ART.
- Section 7.9: clarification of reporting of protocol violations.
- Section 7.9.1: clarification of definition of SAEs and reporting.
- Section 8.1 Table 5: second line ART specified as containing 2 NRTIs rather than limiting to ddi+d4T.
- **Section 8.1.1: revision to allow NORA in Harare.**
- Section 8.1.2: second line ART specified as containing 2 NRTIs rather than limiting to ddi+d4T and removal of reference to Zimbabwe as only country where NVP will be first line.
- Sections 9.1 & 9.4: a subgroup of TSC (not of DSMC) will monitor STI pilot and STI.
- Section 9.5: Endpoint Review Committee structure revised.
- Section 12.0: requirement for locked file cabinets replaced with locked locations.
- Section 14.0 ref 10: update of reference to WHO guidelines from draft to final.
- **Appendix 1.0: monitoring of STI pilot revised.**
- Appendix 1.5: pregnancy test corrected to week 48 from 52.
- Appendix 2.4: NORA schema clarified.
- **Appendix 2.5.1: NORA primary endpoint revised.**
- **Appendix 2.5.2: NORA secondary endpoints clarified.**

- **Appendix 2.6.2 pt 5: replacement of WBC as example exclusion criterion with neutrophils $<0.50 \times 10^9/l$.**
- Appendix 2.9: management of adverse events in NORA expanded.
- Appendix 2.9.5: revision of safety monitoring in NORA.
- Appendix 2.11: NORA flowsheet revised - removal of extra pregnancy test at week 12 and adherence assessment at week 0.
- **Appendix 2.12: NORA patient information sheet revised for inclusion of Harare.**
- **Appendix 2.13: NORA consent revised for inclusion of Harare.**
- Appendix 3.0: removal of restriction for TDF to be taken with food.
- Appendix 3.0: footnote added to ZDV contraindications to note revised eligibility criteria on neutrophils.
- Appendix 5.0: correction of performance scale 3 to bed-ridden $<50\%$ of time.

TABLE OF CONTENTS

1.0 Summary	11
1.1 Abstract	11
1.2 Trial Schema	12
1.3 Flow Sheets	13
2.0 Background and Rationale	17
2.1 Introduction	17
2.2 Monitoring for efficacy and toxicity	17
2.3 Structured Treatment Interruptions (STIs).....	18
2.4 Antiretroviral Therapy Regimens.....	18
2.5 Rationale.....	20
3.0 Objectives	21
3.1 Main DART Trial Objectives.....	21
3.2 STI Pilot Study Objectives.....	21
3.3 Abacavir Safety Substudy <u>N</u> evirapine <u>O</u> R <u>A</u> bacavir (NORA) Objectives.....	21
4.0 Endpoints	21
4.1 Primary Endpoints:.....	21
4.2 Secondary Endpoints:.....	22
5.0 Design	22
5.1 Type of design.....	22
5.1.1 Randomisation to CMO or LCM	22
5.1.2 STI Pilot	22
5.1.3 STIs or continuous ART	23
5.2 Antiretroviral Therapy.....	23
6.0 Patient Population	23
6.1 Inclusion Criteria.....	23
6.2 Exclusion criteria.....	23
6.3 Number and source of subjects	24
7.0 Procedures and Management of Subjects	24
7.1 Screening Procedure.....	24
7.2 Baseline procedure (Week 0)	25
7.3 Randomisation and Enrolment	25
7.3.1 Randomisation List	25
7.3.2 First Randomisation to CMO or LCM.....	25
7.3.3 Second Randomisation – STIs or continuous ART	26
7.3.4 Pregnancy	27
7.3.5 Enrolment of family members into the trial.....	27
7.4 Follow-up Evaluations	27
7.5 Management of patients allocated to the STI arm.....	28
7.5.1 Timing of STIs	28
7.5.2 Criteria for modifying the STI regimen and for restarting ART early.....	29
7.5.3 Deferring STI during follow-up.....	29
7.6 Switching ART.....	30
7.6.1 Switching for Toxicity	30
7.6.2 Switching for failure of first-line therapy	30
7.7 Assessment of adherence	31

7.8	Withdrawal from allocated strategy	31
7.9	Recording and reporting of Adverse Events, Death, HIV progression and protocol violations.....	31
7.9.1	Serious Adverse Events (SAE):	31
8.0	Drug Regimens	32
8.1	Antiretroviral Therapy.....	32
8.1.1	First-line antiretroviral drugs	32
8.1.2	Second-line antiretroviral drugs.....	33
8.1.3	Provision of trial drugs.....	33
8.1.4	Modification of therapy for toxicity	33
8.2	Prophylaxis against Opportunistic Infections	34
8.3	Medications not permitted/ Precautions.....	34
8.4	Data on concomitant medications	34
9.0	Management of the Trial.....	34
9.1	Trial Steering Committee	34
9.2	Trial Management Groups	35
9.3	Data Management and Monitoring	35
9.4	Data and Safety Monitoring Committee (DSMC)	35
9.5	Endpoint Review Committee	36
10.0	Statistics	36
10.1	Sample Size	36
10.2	Analysis Plan.....	37
11.0	Regulatory/ Ethics Approval	38
12.0	Confidentiality.....	38
13.0	Publication	38
14.0	References	38

Appendices

Appendix 1.0	Structured Treatment Interruptions (STI) Pilot Study	40
1.1	Monitoring of individual patients	40
1.2	Monitoring of the group data	40
1.3	Guidelines for management during STI pilot.....	41
1.4	Guidelines for the DSMC and Steering Committees.....	41
1.5	Flow Sheet for STI pilot	42
Appendix 2.0	Nevirapine OR Abacavir (NORA) Substudy	43
2.1	Objective	43
2.2	Background and Rationale	43
2.2.1	Hypersensitivity reaction to Abacavir.....	43
2.2.2	Adverse reactions to NVP	44
2.3	Trial Design	44
2.4	NORA Trial Schema	45
2.5	Endpoints	45
2.5.1	Primary endpoint:.....	45
2.5.2	Secondary Endpoints.....	46

2.6 NORA Criteria for Inclusion/Exclusion	46
2.6.1 Inclusion Criteria.....	46
2.6.2 Exclusion criteria	46
2.7 Sample size	47
2.8 Analysis Plan	47
2.9 Management of Adverse reactions	47
2.9.1 Management of reactions to combivir	47
2.9.2 Management of reactions to blinded drug.....	47
2.9.3 Management of nevirapine reactions	48
2.9.4 Management of abacavir reactions	48
2.9.5 Safety monitoring.....	48
2.10 Hypersensitivity reaction to abacavir and management of safety - as provided by GSK.	49
2.10.1 Description of hypersensitivity to Abacavir	49
2.10.2 Information for patients	50
2.10.3 Medical management for possible hypersensitivity to abacavir	50
2.10.4 Medical management for Abacavir rash <u>not</u> accompanied by systemic symptoms	51
2.10.5 Fever and hypersensitivity to Abacavir	51
2.10.6 Special considerations following an interruption of abacavir therapy.....	51
2.11 NORA SUBSTUDY FLOW SHEET	53
2.12 DART NORA Substudy Patient Information sheet	54
2.13 DART NORA Substudy Patient consent form	56
Appendix 3.0 Details of Antiretroviral Therapy.....	57
Appendix 4.0 Toxicity Grading and Management	61
4.1 Table of Common Toxicity Criteria	61
4.2 Table of Clinical Signs, Symptoms, Monitoring and Management of Symptoms of Serious Adverse Effects of Antiretroviral Drugs that Require Drug Discontinuation (adapted from WHO guidelines ^{ref 10} Annex 11B)	64
4.3 Guide to management of toxicities	65
4.3.1 Grade 1 (clinical or laboratory(LCM arm only)):	65
4.3.2 Grade 2 (clinical or laboratory(LCM arm only)):	65
4.3.3 Grade 3 (clinical or laboratory(LCM arm only)):	65
4.3.4 Grade 4*(clinical or laboratory):	65
Appendix 5.0 Clinical progression and WHO Definitions	67
Appendix 6.0 Patient Information sheet and Consent Forms (Templates)..	68
6.1 Patient information sheet for DART study	68
6.2 Consent for Screening for the DART Trial	72
6.3 Patient consent form for DART Trial	73
Appendix 7.0 Handling and Storage of Specimens.....	74
7.1 Bloods	74
7.1.1 Processing of EDTA blood for Plasma and cell store.....	74
7.1.2 Storage of samples	74
Appendix 8.0 Adherence protocol	75
Appendix 9.0 Post DART Trial issues.....	76

Tables

Table 1	Laboratory and Clinical Monitoring (<u>LCM</u>) group (+/- STI co-enrolment)	13
Table 2	<u>LCM</u> group (+/- STI co-enrolment): weeks 84-180	14
Table 3	Clinical Monitoring Only (<u>CMO</u>) Group (+/- STI co-enrolment)	15
Table 4	<u>CMO</u> Group (+/- STI co-enrolment): weeks 84 - 180	16
Table 5	First and second-line drug regimens for DART (For details see Appendix 3.0, page 57)	32
Table 6	Guidelines for Switching for Toxicity	33
Table 7	STI Pilot for 100 patients (completed 24 weeks in CMO or LCM and with CD4 cell counts at week 24 of 200 cells/mm ³ or higher.	42
Table 8	NORA flow sheet	53

1.0 Summary

1.1 Abstract

The DART protocol describes an open-label randomised trial evaluating two strategic approaches for management of antiretroviral therapy (ART) in symptomatic HIV infected adults in Africa. The first strategy compares **clinical monitoring only** (CMO) with **laboratory plus clinical monitoring** (LCM). The second approach compares structured treatment interruptions (STIs: 12 weeks on, 12 weeks off ART) with continuous ART in patients who achieve CD4 cell counts ≥ 300 cells/mm³ after 48 weeks on continuous ART.

Eligible patients will have symptomatic HIV disease (WHO stage 2, 3 or 4) and CD4 cell counts <200 cells/mm³, no prior ART and no clinical or laboratory abnormalities contra-indicating start of ART. 3300 patients will be enrolled over 1-2 years into the CMO/LCM comparison from 3 African sites (2 in Uganda, 1 in Zimbabwe) and followed for 3-5 years. In both CMO and LCM arms, patients will have haematology and liver function tests performed but the results will not be returned to clinicians caring for patients in CMO arm unless indicative of a grade 4 adverse event. CD4 counts will be performed both in CMO and LCM arms with results not returned to physicians in the CMO arm but monitored independently by a subgroup of the Data Safety and Monitoring Committee (DSMC).

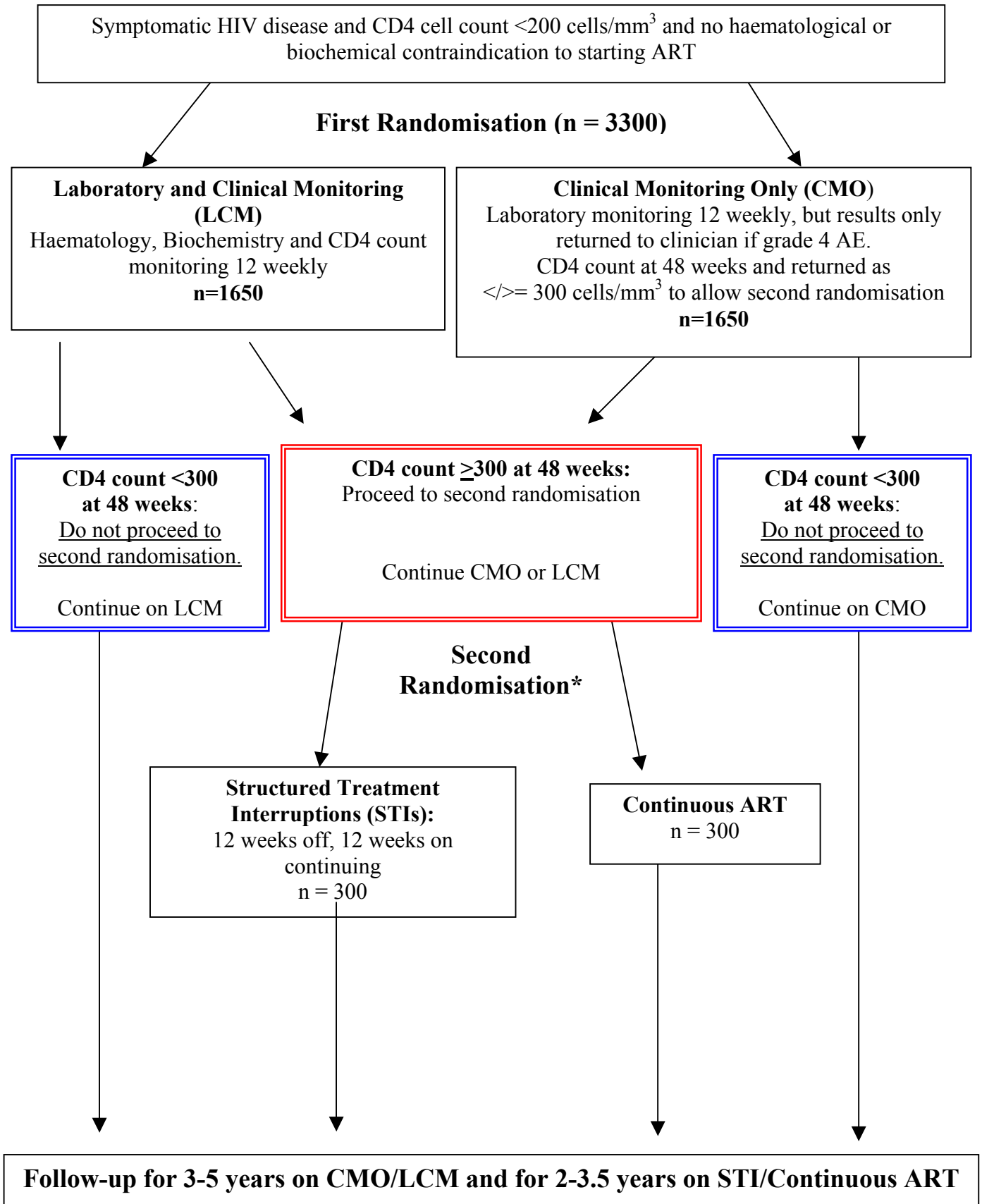
Following the pilot STI study in 100 patients, it is expected at least 600 will achieve CD4 ≥ 300 cells/mm³ by 48 weeks after trial entry and will undergo a second randomisation to structured treatment interruption (STI) or to continuous ART. The second randomisation will open after a non-randomised pilot study of a 100 patients assigned to STIs (see Appendix 1.0, page 40) has been completed and the DSMC and Trial Steering Committees have assessed STIs as safe. During the pilot study and during the first phase of the STI randomisation, all patients (in both CMO and LCM arms) will undergo monthly CD4 cell monitoring.

Patients will initially receive zidovudine (ZDV) and lamivudine (3TC) in combination (combivir) plus tenofovir (TDF, 2,400 patients) or nevirapine (NVP, 300 patients). In addition, six hundred patients enrolled early in the trial will be offered co-enrolment (for which they will consent separately) to a double blind 24-week comparison of the safety of abacavir (ABC) versus NVP for first line therapy (see Appendix 2.0, page 43). These patients will continue to receive ABC or NVP, respectively, after the blinded period is over. For intolerance or toxicity of any individual drug, another ART drug from the same class will be substituted.

The primary efficacy endpoint will be progression to a new WHO HIV stage 4 disease or death. The decision to change to second-line ART will be based on clinical criteria alone for the CMO arm and on clinical plus laboratory criteria for the LCM arm. Second-line ART of two nucleoside reverse transcriptase inhibitors (NRTIs) and either a ritonavir-boosted protease inhibitor (PI), NVP or TDF will be provided, depending on the first-line regimen received. Patients who fail the second-line regimen will be offered the best combination available from the first and second line drugs.

DART is a five-year trial. Recruitment into the trial will take place over two years for the first randomisation to the 2 monitoring strategies, with follow-up of 3 years after the last patient is randomised. For the second randomisation to STIs or continuous ART, recruitment will occur during the second and third years, to be completed by the end of the third year and follow-up will be for up to 2 years after the last patient is randomised.

1.2 Trial Schema



* Once second randomisation has opened after STI pilot

1.3 Flow Sheets

Table 1 Laboratory and Clinical Monitoring (LCM) group (+/- STI co-enrolment)

EVENTS	WEEK IN TRIAL																						
	Start therapy Week 0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	
Doctor/Nurse visit * <input type="checkbox"/>																							
Nurse visit <input type="checkbox"/>																							
Doctor only visit * <input type="checkbox"/>																							
CD4 >= 300 at week 48																							
Adherence assessment and 4 weeks ART supply *																							
Consent to screening and patient information sheet	X																						
Informed Consent																							
History & Physical ¹	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom check list	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test ²																							
Haematology ³			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biochemistry ⁴			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lymphocyte Subsets ⁵	X																						
Plasma storage ⁶	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* Patients will return 4-weekly to see the nurse or doctor, return used drug containers and receive 4 weeks of ART (except for STI). Nurse should check if patient has any new symptoms since the last visit. If yes, patient should see the trial doctor BEFORE PROCEEDING with structured treatment interruption (STI). The doctor will prescribe antiretroviral therapy and make decisions on any modifications of therapy as necessary.

- Clinical: including weight, WHO staging for HIV.
- At screening, and subsequently at start of STI in those randomised to STI; see section 7.3.4 if positive.
- Haematology: Hb, MCV, WBC, Lymphocytes, Neutrophils, and Platelets.
- Biochemistry: Urea, Creatinine, AST or ALT, Bilirubin
- CD4, CD8, CD3 percentage and absolute, total lymphocyte count
- Take 6 ml EDTA blood. Store DNA pellet at week -2, 0, 24, 48 and then every 48 weeks (if feasible). See Appendix 7.0 for instructions about storage. Take plasma (DNA pellet if feasible) at time of switch. Take plasma as near as possible to time of delivery for any women giving birth in DART

Table 2 LCM group (+/- STI co-enrolment): weeks 84-180

EVENTS	WEEK IN TRIAL																										
	84	88	92	96	100	104	108	112	116	120	124	128	132	136	140	144	148	152	156	160	164	168	172	176	180	12** weekly	
Doctor/Nurse visit * <input type="checkbox"/>	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART	Restart ART
Nurse visit <input type="checkbox"/>	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI	Start STI
CD4>=300 at week 48	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	STI or X	
Adherence assessment and 4 weeks ART supply*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Informed Consent																											
History & Physical ¹			X				X			X			X			X			X			X			X		
Symptom check list	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test ²				X						X					X				X			X			X		
Haematology ³	X			X			X			X			X			X			X			X			X		
Biochemistry ⁴	X			X			X			X			X			X			X			X			X		
Lymphocyte Subsets ⁵	X			X			X			X			X			X			X			X			X		
Plasma storage ⁶	X			X			X			X			X			X			X			X			X		

* **Patients will return 4-weekly to see the nurse or doctor, return used drug containers and receive 4 weeks of ART (except for STI).**

The doctor will prescribe antiretroviral therapy and make decisions on any modifications of therapy as necessary.

¹ Clinical: including weight, WHO staging for HIV

² At screening, and subsequently at start of STI in those randomised to STI; see section 7.3.4 if positive.

³ Haematology: Hb, MCV, WBC, Lymphocytes, Neutrophils, and Platelets

⁴ Biochemistry: Urea, Creatinine, AST or ALT, Bilirubin

⁵ CD4, CD8, CD3 percentage and absolute, total lymphocyte count

⁶ Take 6 ml EDTA blood. Store DNA pellet at week 96 and then every 48 weeks (if feasible). See Appendix 7.0 for instructions about storage. Take plasma (DNA pellet if feasible) at time of switch. Take plasma as near as possible to time of delivery for any women giving birth in DART

Table 3 Clinical Monitoring Only (CMO) Group (+/- STI co-enrolment)

EVENTS	WEEK IN TRIAL																						
	Start therapy Week 0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	
Doctor/Nurse visit* <input type="checkbox"/>																							
Nurse visit <input type="checkbox"/>																							
Doctor only visit* <input type="checkbox"/>																							
CD4 >=300 at week 48																							
Adherence assessment and 4 weeks drug supply*																							
Consent for screening and patient information	X																						
Informed consent	X																						
History & Physical ¹	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom check list	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test ²																							
Haematology ³	X																						
Biochemistry ⁴	X																						
Lymphocyte Subsets – results returned to clinician ^{5a}	X																						
Lymphocyte Subsets – results not returned to clinician ^{5b}																							
Plasma storage	X																						

* Patients will return 4-weekly to see the nurse or doctor, return used drug containers and receive 4 weeks of ART (except for STI). Nurse should check if patient has any new symptoms since the last visit, if yes patient should see the trial doctor BEFORE PROCEEDING with structured treatment interruption (STI). The doctor will prescribe antiretroviral therapy and make decisions on any modifications of therapy as necessary.

¹ Clinical: including weight, WHO staging for HIV.
² At screening, and subsequently at start of STI in those randomised to STI; see section 7.3.4 if positive
³ **Blinded** Haematology: Hb, MCV, WBC, Lymphocytes, Neutrophils, Platelets, except at screening (week -2) when results returned to clinician.
⁴ **Blinded** Biochemistry: Urea or Creatinine, AST or ALT, Bilirubin, except at screening (week -2) when results returned to clinician
^{5a} Return results at baseline. At week 48 return result as </>=300 cells/mm³. If result at week 48 is >=300 cells/mm³, randomise to STI or no STI. A result taken at time of switch to second-line therapy should not be made available to clinician. After switch, all patients receive at least 48 weeks of continuous ART. At the next scheduled visit where lymphocyte subsets are taken prior to a scheduled STI but at least 48 weeks post switch, CD4 cell count will again be made available to the clinician (as </>=300 cells/mm³). If this result is >=300 cells/mm³, patients in the STI arm may recommence STI. If CD4 count is <300 cells/mm³, then patient continues ART with no further STI.
^{5b} **Blinded** CD3, CD4, CD8 percentage and absolute, total lymphocyte count.
⁶ Take 6 ml EDTA blood. Store DNA pellet at week -2, 0, 24, 48 and then every 48 weeks (if feasible). See Appendix 7.0 for instructions about storage. Take plasma at time of switch (and DNA pellet if feasible). Take plasma as near as possible to time of delivery for any women giving birth in DART

Table 4 CMO Group (+/- STI co-enrolment): weeks 84 - 180

EVENTS	WEEK IN TRIAL																											
	84	88	92	96	100	104	108	112	116	120	124	128	132	136	140	144	148	152	156	160	164	168	172	176	180	12** weekly		
Doctor/Nurse visit * <input type="checkbox"/>																												
Nurse visit <input type="checkbox"/>																												
CD4 >=200 at week 48																												
Adherence assessment and 4 weeks drug supply*	STI	Restart ART	X	X	STI	Restart ART	X	X	STI	Restart ART	X	X	STI	Restart ART	X	X	STI	Restart ART	X	X	STI	Restart ART	X	X	STI	Restart ART	X	X
	OR				OR				OR				OR				OR			OR				OR			OR	
	X		X	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X	
Informed Consent																												
History & Physical ¹	X			X			X			X			X			X			X			X			X		X	
Symptom check list	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test ²			X						X						X				X			X						
Haematology ³	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Biochemistry ⁴	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Lymphocyte Subsets- return results to clinician ^{5a}																												
Lymphocyte Subsets- do not give results to clinician ^{5b}	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Plasma storage ⁶	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

* **Patients will return 4-weekly to see the nurse or doctor return used drug containers and receive 4 weeks of ART (except for STI). The doctor will prescribe antiretroviral therapy and make decisions on any modifications of therapy as necessary.**

¹ Clinical: including weight, WHO staging for HIV.
² At screening, and subsequently at start of STI in those randomised to STI; see section 7.3.4 if positive
³ **Blinded** Haematology: Hb, MCV, WBC, Lymphocytes, Neutrophils, Platelets, except at screening (week -2) when results returned to clinician
⁴ **Blinded** Biochemistry: Urea or Creatinine, AST or ALT, Bilirubin, except at screening (week -2) when results returned to clinician
^{5a} Return results at baseline. At week 48 return result as </>=300 cells/mm³. If result at week 48 is >=300 cells/mm³, randomise to STI or no STI. A result taken at time of switch to second-line therapy should not be made available to clinician. After switch, all patients receive at least 48 weeks of continuous ART. At the next scheduled visit where lymphocyte subsets are taken prior to a scheduled STI but at least 48 weeks post switch, CD4 cell count will again be made available to the clinician (as </>=300 cells/mm³). If this result is >=300 cells/mm³, patients in the STI arm may recommence STI. If CD4 count is <300 cells/mm³, then patient continues ART with no further STI.
^{5b} **Blinded** CD3, CD4, CD8 percentage and absolute, total lymphocyte count. .
⁶ Take 6 ml EDTA blood Store DNA pellet at week -2, 0, 24, 48 and then every 48 weeks (if feasible). See Appendix 7.0 for instructions about storage. Take plasma at time of switch and DNA pellet if feasible. Take plasma as near as possible to time of delivery for any women giving birth in DART

2.0 Background and Rationale

2.1 Introduction

The prevalence of HIV infection is very high (>20%) and still rising in many Sub-Saharan African countries. Prevention messages in the absence of treatment appear to have limited impact and the effect of the epidemic on the social and physical well-being of individuals and on the economy of these countries is devastating. Combination antiretroviral therapy (ART) has had a dramatic effect on the morbidity and mortality of HIV-infected adults and children in well-resourced countries. It may also reduce transmission of HIV, through reduction in HIV viral load. Until recently very high costs were an absolute barrier to the introduction of ART on a wide scale in resource-poor countries. However, these have recently been reduced substantially, making the provision of ART to HIV-infected persons in Africa a realistic possibility. However, the costs and infrastructure required for monitoring patients taking these drugs for efficacy and toxicity, as carried out in developed countries, are also extremely high. There are concerns about the lack of infrastructure to administer ART and to sustain adherence and monitor toxicity in developing country settings. Trials are needed to evaluate strategies for using ART, which are tailored to the circumstances of developing countries.

DART aims to address two major questions. The first is whether ART can be safely given with clinical monitoring alone, in the absence of regular viral load and CD4 measurements and laboratory monitoring for toxicity. The second question concerns the use of pulse compared with continuous ART, the hypothesis being that pulse therapy would reduce the cost and toxicity of ART and may improve adherence, without increasing the risk of developing resistance or disease progression.

2.2 Monitoring for efficacy and toxicity

In persons starting ART in well-resourced countries, monitoring of prognostic markers of HIV disease (HIV RNA viral load and CD4 cell counts) is routinely undertaken in order to make decisions about starting and switching therapy. In addition, routine monitoring of laboratory markers is undertaken in order to detect bone marrow, liver and other toxicities to ART.

Although trials have been carried out, and others are currently ongoing, to ascertain the value of resistance testing in the management of HIV, no trials have been undertaken in developed countries to determine the efficacy and cost-effectiveness or the optimum frequency of HIV RNA viral load or CD4 count monitoring. There have been no studies evaluating the need for, or frequency of laboratory tests required for monitoring toxicity of ART. HIV RNA and CD4 count tests are particularly expensive (although the cost may come down), and unavailable outside major centres in Africa. In addition there are important issues of quality control. Requirements for monitoring schedules similar to those in developed countries are likely to be a barrier to the administration of ART to large numbers of persons in the African setting. Although HIV RNA viral load is an important prognostic marker and is widely used to monitor therapy when first introduced, recently greater emphasis has been placed on monitoring CD4 cell counts as these are better predictors of the immediate risk of clinical disease progression and mortality, particularly in late disease. Furthermore, with the current therapeutic options, it is difficult to maintain HIV RNA below the limit of detection of

current assays, over a long period of time, although CD4 count increases may be maintained. Many would therefore agree that HIV-RNA viral load monitoring is unlikely to be cost-effective or necessary in the African setting. However, it is unclear whether decisions about management of ART toxicity or switching ART can be made on the basis of clinical signs and symptoms alone, or should be on the basis of clinical monitoring plus regular laboratory monitoring for toxicity and CD4 cell counts.

2.3 Structured Treatment Interruptions (STIs)

Structured Treatment Interruptions (STIs), whereby periods on ART are followed by periods off treatment, are being explored in a number of circumstances in developed countries. First, following recent infection with HIV, there is some evidence from small uncontrolled studies that STIs lead to control of viral replication even during periods of no therapy in some patients [1-4]. Second, in patients who have failed several ART regimens and have resistant virus, there is some evidence that an STI leads to the re-emergence of wild-type sensitive virus which may result in a better response to a subsequent new ART regimen [5, 6]; this is being explored in ongoing randomised trials (e.g. OPTIMA Trial). Finally, in chronically infected patients, the possibility of reducing toxicity, improving adherence and reducing costs, while maintaining the clinical and immunological well-being of patients has been reported in observational studies of STI [7,8].

Different periods of interruption of ART are being explored in a number of trials of pulse compared with continuous ART in patients with suppressed viral replication in developed countries. One approach is to cycle on and off ART rapidly (7-days on, 7-days off). This has been reported in small studies to prevent an increase in viral load and the re-emergence of resistance, but may be difficult to implement. Other approaches being evaluated include longer cycles (e.g. 1, 2, 3 or 4 months on and off therapy), and trials where the length of treatment interruption is individualised and driven by the rate of fall in CD4 cell count after stopping ART (e.g. TILT Trial). To date, no evidence is available to define the most appropriate approach. This may anyway be different in the African setting, where many patients are likely to start ART with much lower CD4 cell counts than in developed countries and where CD4 count monitoring is expensive and not readily available. The limited data available from STI studies suggest that the average fall in CD4 count is about 20 cells a month, but may be faster, up to 50-60 cells/month [9], in patients starting ART with a very low CD4 count.

STI trials in developed countries aim to keep CD4 cell counts above a threshold of 200 cells/mm³. However, most opportunistic infections occur when the CD4 count falls below 50 cells/mm³. It would be unreasonable not to start ART in patients in most need in Africa, nearly all of whom will have symptomatic disease and many of whom will have CD4 counts below 50 cells/mm³. It could be argued that it would not be appropriate to interrupt ART until CD4 has increased to above 200 cells/mm³.

2.4 Antiretroviral Therapy Regimens

The role of regular CD4 count monitoring could not be evaluated if the trial did not incorporate a second line ART regimen. The choice of first-line therapy is in line with recently developed WHO guidelines on the use of antiretroviral therapy in resource-poor settings [10]. These recommend use of a double NRTI plus an NNRTI or a triple NRTI

regimen, preserving PI-containing regimens for a second-line regimen. The key questions being addressed in the DART trial do not necessitate the use of the same first-line regimen for all patients in the trial. Further, including more than one first-line regimen would enhance the generalisability of results.

2NRTI + NNRTI Regimens

Possible options for this first-line regimen include combivir (zidovudine and lamivudine) plus an NNRTI; e.g. nevirapine (NVP) or efavirenz (EFZ). Both combinations have proven first line efficacy. Efavirenz may be teratogenic if used in pregnancy, which would be a major issue for women of childbearing age. Nevirapine (NVP) is being used increasingly as a single dose in women during labour (and one dose to the baby at birth) to reduce mother-to-child HIV transmission (MTCT) and it is unclear to what extent the widespread use of NVP for treatment could impact MTCT programs. Further, if women have already received NVP during a previous pregnancy, it is possible (although unproven) that its subsequent efficacy as part of a treatment regimen may be reduced, as it is known that resistance can develop rapidly. Both NVP and Efavirenz have long half-lives and resistance develops rapidly. Stopping the NNRTI some days before the NRTIs during treatment interruptions therefore needs to be considered. It is planned to obtain additional pharmacokinetic data to facilitate best management of this issue.

Triple NRTI Regimens

The formulation of a triple NRTI combination of zidovudine, lamivudine and abacavir (trizivir), given as one tablet twice a day, provides the possibility of a well-tolerated, simple regimen with the advantage that there is a reduced possibility of developing resistance (as all drugs are in one tablet) and there are likely to be fewer interactions with other drugs (e.g. anti-tuberculosis drugs) than with other anti-HIV drugs, particularly protease inhibitors. However, trizivir has potential hazards related to abacavir (ABC), which is associated with hypersensitivity in about 3% of patients. This can be fatal if the patient is re-challenged after stopping the drug for symptoms of hypersensitivity. There is no evidence that interruption of therapy not preceded by hypersensitivity symptoms leads to problems but there are relatively few data on this. Any patient stopping abacavir for hypersensitivity would need to receive a replacement drug and would then have to take therapy as separate formulations (two formulations if using combivir (ZDV+3TC combined) or three if all three drugs are provided separately). Giving abacavir as part of a regimen with STIs will require close monitoring, particularly in the early phase of treatment. However, the symptoms of hypersensitivity to abacavir are predominantly clinical (fever and rash) and careful monitoring will ensure safety of patients.

Information on whether symptoms of immune reactivation post ART or symptoms of tropical diseases could be mistaken for the toxicity of abacavir, when used in combination with combivir (ZDV+3TC) or as trizivir, will be valuable in terms of the widespread use of this combination in developing countries and will be obtained from the NORA substudy in the DART trial (see Appendix 2.0, page 43).

Other possible triple NRTI regimens include combivir plus didanosine (ddI) or combivir plus a nucleotide reverse transcriptase inhibitor, tenofovir (TDF). TDF is available as a single tablet to be taken once daily. It has an excellent safety profile, and has recently been shown to have efficacy at least similar to NRTIs in a 48-week trial comparing the effect on HIV RNA of D4T+3TC+EFV with that of TDF+3TC+EFV [11]. In addition, HIV resistance against

TDF develops very slowly, making it an attractive drug to use in resource-poor settings in the absence of HIV RNA resistance testing.

2.5 Rationale

The DART trial is addressing a very important question about safe management of patients taking ART in an environment where routine toxicity and efficacy tests may not be available in compliance with the principles of Good Clinical Practice and the Declaration of Helsinki.

In the African setting, many patients adopt a practice of interrupting therapy because of limited funds. However, this is usually done in a haphazard way and it is unclear whether it is safe. STI trials are being undertaken in chronic HIV infection in developed countries with the aims of reducing toxicity, costs, and possibly improving adherence, without compromising efficacy. In Africa reduction of costs, in particular, would have major advantages. However, as the natural history of HIV in Africa differs from that in developed country settings (e.g. a much higher proportion of TB) and patients are likely to start ART later in the course of HIV disease, it is necessary to evaluate the safety of STI in an African setting. The optimum period for STI is not yet known but rapid cycling of drugs would be too complex. A 3-month cycle has been chosen for DART but may be altered following data from the pilot phase (see Appendix 1.0, page 40).

ART administration in developed countries is accompanied by tests for monitoring ART efficacy and toxicity. However, no trials evaluating the need for laboratory monitoring over and above clinical monitoring alone have been undertaken in developed countries. The cost of tests to measure CD4 cell count, and also of haematology and liver function tests is a major barrier to administration of ART to large numbers of persons in resource-poor settings. Even if costs are reduced, these tests are unlikely to be available outside major centres. Therefore there is a need to explore the question of the necessity of these laboratory tests with the introduction of ART in Africa.

The advantages of combining both the STIs and monitoring questions into a three-centre trial are 3-fold: first, a larger trial can be undertaken than would be possible in a single clinical centre; second, the logistics of supplying drugs for a single trial to address both questions, rather than two separate trials, would be simpler and cheaper; thirdly, collaboration across sites in Africa would be likely to build capacity and enhance regional knowledge about the use of ART.

A simple ART regimen is important for use in the African setting. At a recent meeting of HIV experts at WHO to develop guidelines on use of ART in resource-poor countries, the combination of ZDV, 3TC and ABC in one preparation (trizivir) was considered as a front-runner for first-line therapy because of ease of administration (one pill twice daily), and lack of interaction with other drugs, in particular anti-TB drugs [10]. However, although there is good data to guide the management of hypersensitivity reactions to ABC in developed countries, this may be different in the African setting because immune reconstitution syndromes may be more common after starting ART in patients with advanced disease living in areas with high prevalence of other infectious diseases. A 600-patient, double blind substudy comparing the toxicity of ABC and NVP (both given with combivir) will therefore be undertaken within the DART trial (see Appendix 2.0, page 43). (This will require placebos for both NVP and ABC.) For the remaining patients in the main study (2700 patients), combivir + TDF will be the first-line regimen for 2400 patients and combivir + NVP for 300 patients.

For second-line therapy, two new NRTIs plus a ritonavir-boosted PI (most probably saquinavir or lopinavir) will be used, although for the 600 patients enrolled in the substudy, didanosine (ddI) + stavudine (d4T) + TDF could be used.

3.0 Objectives

3.1 Main DART Trial Objectives

To compare, in terms of clinical HIV disease progression or death:

1. Clinical monitoring only (CMO) versus routine regular laboratory and clinical monitoring (LCM)
2. Structured Treatment Interruptions (STIs: 12 weeks on, 12 weeks off therapy) versus continuous ART, initiated if the CD4 count has increased to above 300 cells/mm³ (after 48 weeks on ART).

The hypothesis is that CMO will result in similar outcomes to LCM, and that ART administered as pulse therapy (STI) will result in similar outcomes to continuous ART, in terms of progression of clinical HIV disease or death.

3.2 STI Pilot Study Objectives

The initial non-randomised pilot study of STIs will inform on the safety of the 12 weeks on, 12 weeks off STI strategy (see Appendix 1.0, page 40) and only after the completion of this substudy will the second randomisation commence.

3.3 Abacavir Safety Substudy Nevirapine OR Abacavir (NORA) Objectives

This randomised sub-study of 600 patients will address issues of safe administration of abacavir (ABC) in resource poor settings and will compare the safety of ABC with that of NVP when used in combination with combivir (see Appendix 2.0, page 43).

4.0 Endpoints

4.1 Primary Endpoints:

- *Efficacy*: Progression to a new WHO stage 4 HIV event or death (see Appendix 5.0, page 67).
- *Safety*: Any serious adverse event, which is not HIV related (see section 7.9, page 31 and Appendix 4.0, page 61).

4.2 Secondary Endpoints:

- Progression to a new or recurrent WHO stage 4 HIV event or death
- Progression to a new WHO stage 4 HIV event or death from 6 weeks after randomisation
- Progression to a new or recurrent WHO stage 4 HIV event or death from 6 weeks after randomisation
- Any grade 3 or 4 adverse events (see Appendix 4.0, page 61)
- Number and class of anti-HIV drugs received by 3 years
- Time to cessation of first-line regimen for failure
- Adherence as measured by questionnaire and pill counts
- CD4 count at 3 years (provided that it is at least 2 months after restarting ART for those in the STI group)
- HIV RNA viral load (performed retrospectively) at 3 years (providing that it is at least 2 months after restarting ART for those in the STI group)
- HIV resistance profiles at 3 years in those with detectable viral load (providing that it is at least 2 months after restarting ART for those in the STI group)

5.0 Design

5.1 Type of design

DART is an international, three-centre open-label randomised trial in symptomatic HIV infected adults in Africa. There will be two randomisations and the total duration of the trial will be 5 years.

5.1.1 Randomisation to CMO or LCM arm

3300 patients will be randomised to CMO or LCM over a period of two years. Randomisation will be stratified by CD4 count (0-99, 100-199) and by clinical sites.

5.1.2 STI Pilot

Because there are no data on STI in the African setting, where patients are likely to have low CD4 cell counts before starting ART, a non-randomised pilot study of the first 100 patients eligible for the STI randomisation will be undertaken (see Appendix 1.0, page 40). This would be expected to delay the onset of the second randomisation by a minimum of 6 months (the time taken to enrol patients (estimated to be 2-3 months), and at least 3 months follow-up). During this 24-week period the patients will be seen by the doctor every 4 weeks and 4-weekly CD4 cell counts will be performed on all 100 patients and reported to the clinicians in the LCM arm and to the subgroup of DSMC in the CMO arm

5.1.3 STIs or continuous ART

Of the 3300 patients randomised to CMO or LCM, we would expect at least 600 to be eligible for the second randomisation (STIs versus continuous ART) commencing after the STI pilot (see section 5.1.2 above and Appendix 1.0, page 40), which should be completed by about 12 months after the start of the trial. Randomisation to STIs or continuous ART would be completed by the end of year 3.

5.2 Antiretroviral Therapy

See section 8.0, page 32 and Appendix 3.0, page 57 for full details. First and second-line regimens will be available for all patients as well as the option of changing individual drugs (within the same class) for toxicity (see sections 7.6, page 30 and 8.0, page 32, Appendix 3.0, page 57 and Appendix 4.0, page 61). For patients in whom second-line therapy fails, the most appropriate combination of available drugs will be offered (see section 8.0, page 32). Every effort will be made to make further ART available after the trial but it is agreed that local health authorities will commit to providing adequate care for the participating patients (see Appendix 9.0, page 76).

6.0 Patient Population

6.1 Inclusion Criteria

1. Documentation of HIV-1 infection: antibody positive serology by ELISA test (confirmed by licensed second ELISA or Western Blot).
2. Age \geq 18 years
3. Symptomatic WHO stage 2, 3 or 4 HIV disease ***and*** CD4 $<$ 200 cells/mm³
4. ART naïve (except for ART use during pregnancy for the prevention of mother-to-child HIV transmission).
5. Agreement and documented informed consent to be randomised to CMO or LCM and to STI or continuous ART, if eligible.
6. Life expectancy of at least 3 months.

6.2 Exclusion criteria

1. Cannot, or unlikely to attend regularly (e.g. usual residence too far from Study Centre)
2. Likelihood of poor compliance
3. Presence of acute infection (e.g. malaria, acute hepatitis, pneumococcal pneumonia, non-typhoid salmonella septicaemia, cryptococcal meningitis). Patients may be admitted after recovery of an acute infection. Patients with tuberculosis (TB) will not be enrolled while on the intensive phase of anti-tuberculosis therapy, but should be re-evaluated after the intensive phase and a decision made then about starting ART. Patients starting ART whilst on anti-tuberculosis therapy after the intensive phase will not receive NVP, nor will they be randomised into the NORA substudy.

4. On chemotherapy for malignancy
5. Laboratory abnormalities which are a contra-indication for the patient to start ART (e.g. Haemoglobin <8g/dl, neutrophils <0.50x10⁹/l, AST or ALT >5 x the upper limit of normal (ULN), grade 3 renal dysfunction - creatinine >360 µmol/l and/or urea >5 x ULN).
6. Pregnancy or breast-feeding

6.3 Number and source of subjects

Patients will be recruited from three sites: Entebbe Uganda, Kampala Uganda; and Harare Zimbabwe. It is expected that approximately 1000 patients will be recruited from each site, plus 300 from a satellite clinic in Kampala (Academic Alliance). The STI pilot (see Appendix 1.0, page 40) will be conducted in all three sites. The NORA substudy (see Appendix 2.0, page 43) will be conducted in Entebbe and Kampala.

This trial requires that patients commit to long-term follow-up. Therefore priority will be given to those who can regularly attend for follow-up. Patients will be recruited from 3 sources:

1. patients who have been tested for HIV infection in the past and are in regular follow-up;
2. following *recovery* from a hospital admission during which HIV infection has been diagnosed, and followed by attendance at a follow-up outpatient clinic (N.B. no patient should be recruited during a hospital admission);
3. from outpatient clinics (e.g. general medical, TB clinics). For newly HIV diagnosed patients, the HIV counselling and testing process will be fully carried out.

To avoid inequity in access to the trial, the recruitment will be carried out as eligible patients visit the outpatient clinics to consult over a recent health problem or who come for a previously scheduled follow up visit.

7.0 Procedures and Management of Subjects

7.1 Screening Procedure

At screening, HIV infected adults will be given an information sheet about the DART trial and asked to give consent to screening (see Appendix 6.0, page 68). Interested patients will have clinical information including medical history, examination, confirmation of WHO stage 2, 3, or 4, and weight recorded, and T cell subsets (CD4, CD8, CD3 and total lymphocyte count), haematology, biochemistry and pregnancy tests performed. Plasma and DNA pellets will be saved. Women of reproductive age will be given information about the risks of pregnancy in the trial and encouraged to avoid pregnancy.

7.2 Baseline procedure (Week 0)

The time between screening and randomisation should preferably be within 2 weeks and not exceed 4 weeks.

Patients eligibility for enrolment will be confirmed. Patients with CD4 ≥ 200 cells/mm³ can be enrolled later if the CD4 count falls to < 200 cells/mm³ and they are still in follow up. Those in whom the CD4 count is < 200 cells/mm³, with no haematological or biochemistry contraindications to starting ART, will be eligible for the trial.

Fully informed signed consent will be obtained just before randomisation (see Appendix 6.0, page 68). The patient must consent to both randomisations and agree to participate in the STI pilot if required (see Appendix 1.0, page 40). Consent forms should be kept securely at the clinical site and be available for monitoring.

When possible, and particularly if there is doubt about the place of residence of a patient, a study nurse/field worker, preferably the same nurse who gave information about the trial to the patient, will accompany the patient home and draw a map indicating the place of residence.

A trial register should be kept at the clinical site and will record all patients who are eligible and invited to join the trial. Those accepting will have name, date of birth (DOB), date of randomisation and trial number recorded. Those who refuse will have name, DOB, and reason for refusal recorded. The register will be kept in a secure place in each clinical site and will be the responsibility of the trial investigator at that site.

7.3 Randomisation and Enrolment

7.3.1 Randomisation List

A randomisation list for CMO/LCM will be prepared, by computer staff at MRC CTU under the direction of the trial statistician. Patient randomisation numbers will be prepared separately for each centre and further stratified within centre by baseline CD4 cell count (0-99, 100-199). A single member of staff at each site who is not directly involved in patient care will be responsible for carrying out the randomisation process using a secure electronic system. A reliable back-up system will also be available. Randomisation will not take place until after the patient has given informed consent and is ready to receive therapy.

A randomisation list will be similarly prepared for STI/continuous ART after completion of the STI pilot. This will be stratified by centre, by week number at entry (52 or 76, see section 7.3.3 below), and by first randomisation to CMO/LCM.

7.3.2 First Randomisation to CMO or LCM

The first randomisation is to CMO or LCM. The patient's eligibility for enrolment will be reviewed by the doctor at baseline (week 0, see Flow Sheets, section 1.3, page 13), having completed the screening CRF, including all laboratory results. Patients should start ART and be told their allocation on the day of randomisation. Those allocated to LCM will have CD4 cell counts undertaken 12-weekly and haematology and biochemistry tests undertaken at 4, and 12 weeks, and 12-weekly thereafter (see Flow Sheets, section 1.3, page 13).

7.3.3 Second Randomisation – STIs or continuous ART

The second randomisation **will not commence** until the pilot STI study has been completed (see Appendix 1.0, page 40). To determine whether a patient is eligible for the second randomisation, CD4 counts will be undertaken in all patients irrespective of the monitoring arm, at 48 weeks (or at 72 weeks if the patient is beyond 48 weeks when STI randomisation opens) and the results will be returned to the clinician. For patients allocated to CMO, these results will be reported as $CD4 < 300$ or ≥ 300 cells/mm³. Eligibility for the second randomisation will depend on the CD4 cell count being 300 cells/mm³ or higher. If the CD4 count is < 300 cell/mm³ at 48 weeks (72 weeks if the patient is beyond 48 weeks when STI randomisation opens), the patient will **not be eligible** for the second randomisation, but will continue to be followed for the evaluation of the monitoring strategies (see Trial Schema, section 1.2, page 12).

As the results of the STI pilot study have been reviewed by the Trial Steering Committee and Data and Safety Monitoring Committee (DSMC), and STI is still deemed to be safe (see Appendix 1.0, page 40), subsequent patients who are clinically well with CD4 cell counts of 300 cells/mm³ or higher at 48 weeks (72 weeks if the patient is beyond 48 weeks when STI randomisation opens) will be allocated in a 1:1 ratio to continuous ART or to ART with STI (12 weeks off followed by 12 weeks on ART, repeating the schedule until the end of the trial).

Inclusion Criteria:

1. CD4 count 4 weeks prior to STI randomisation visit ≥ 300 cells/mm³

Exclusion criteria:

1. Pregnant or breast-feeding
2. WHO stage 3 or 4 illness in the 12 weeks prior to STI randomisation visit
3. Participation in the STI pilot study

Patients will return to the clinic at week 52 (or week 76 if the patient is beyond 48 weeks when STI randomisation opens), four weeks after the week 48 (or 72) CD4 cell count has been taken. Eligible patients will see the doctor at this visit (see Flow Sheets, section 1.3, page 13). They will be told that they are eligible to be included in the second randomisation, and will be randomised at that visit to the continuous ART arm or the STI arm. They will be requested to bring all unused medication with them, which will be taken from them if they are in the STI arm. If the doctor has clinical concerns about the patient at this visit, such that he/she feels that the STI should not commence despite the CD4 cell count being ≥ 300 cells/mm³ four weeks previously, then he/she may defer randomisation and record using the appropriate form. In all patients undergoing the second randomisation and randomised to STI, this should commence immediately and should be within 5 weeks of the week 48 (or 72) CD4 cell count test (see Trial Schema, section 1.2, page 12 and Flow Sheets, section 1.3, page 13). NVP will be stopped seven days before combivir to avoid the risk of developing NVP resistance because of its long half-life. In practice NVP will be stopped on the day of commencement of STI and combivir alone continued for 7 more days.

The first 100 patients randomised to STI or CT will have plasma stored and CD4 cells measured 4 weekly, including at the time of randomisation; these counts will only be returned to clinicians for LCM patients. Two members of the TSC who are not involved with clinical management of DART patients will closely monitor individual CD4 counts and any WHO 3 and 4 events for these 100 patients on a monthly basis, **without** knowledge of CMO/LCM

allocation. They could decide whether they need to inform the DSMC and TSC immediately, prompting a full analysis of all data accrued in the STI randomisation to this point in time for urgent consideration by the DSMC.

7.3.4 Pregnancy

Eligible women who are found to be pregnant at screening may be rescreened to ascertain eligibility to be enrolled in the trial after the baby is born and breast-feeding has finished, provided that enrolment is still open in that site.

7.3.5 Enrolment of family members into the trial

If more than one person from the same family is eligible and gives consent to enrolment in the trial, they will be allocated to CMO or LCM without consideration as to the randomisation of the family member already enrolled. The same will be true for the STI/continuous ART randomisation. This must be fully explained to family members where more than one is recruited into the trial..

No patient will be enrolled into NORA if there is already a household member in NORA.

7.4 Follow-up Evaluations

After randomisation (week 0) all patients will have follow-up visits to see both the study doctor and study nurse at weeks 2, 4, 8, 12 and then every 12 weeks from randomisation. The patient will collect a supply of drugs every 4 weeks from the nurse at the follow-up and intermediate visits (see Flow Sheets, section 1.3, page 13). For patients randomised to the STI arm, for the first 2 visits at start of STIs (weeks 52 and 76 or 76 and 100), patients will see both a doctor and a nurse at an extra visit, in order for decisions to be endorsed by the doctor about undertaking the next STI (see Flow Sheets, section 1.3, page 13).

At each full assessment, the following will be undertaken (see Flow Sheets, section 1.3, page 13):

- ◆ Administration of a symptom checklist by a nurse to detect intercurrent illness, HIV disease progression or adverse events to ART. The severity and likely relationship of events to ART, will be documented by a doctor.
- ◆ Medical history since last visit including signs and symptoms of HIV disease and WHO stage.
- ◆ Weight.
- ◆ Haematology and biochemistry (as at baseline). However, for patients in the CMO arm; for haematology grade 4 results (see Appendix 4.0, page 61), only the grade 4 result will be returned to the clinic; for biochemistry, if any of AST/ALT/bilirubin are grade 4, all 3 results will be returned to the clinic and, if either of urea/creatinine are grade 4, both will be returned to the clinic. Clinicians may request biochemistry and/or haematology investigations for patients in the CMO arm who experience symptoms suggestive of severe toxicity to antiretroviral drugs they are receiving if the test result is essential in order to make decisions about clinical management (including switching drugs for toxicity, e.g. suspected hepatitis (biochemistry), renal disease (biochemistry), pancreatitis (biochemistry)). Reasons for requesting laboratory tests must be clearly stated on the appropriate form.

- ◆ CD4 cell counts (in the CMO arm, results will not be returned to the clinician except at 48 weeks (72 weeks if the patient is beyond 48 weeks when STI randomisation opens) as <300 or ≥300).
- ◆ Plasma store and DNA pellets (see Appendix 7.0, page 74); stored plasma samples and DNA pellets may be used subsequently for HIV RNA viral load measurements, measurements of cell associated HIV DNA, HIV/HLA typing and analyses of drug levels.
- ◆ Assessment of adherence by pill counts and nurse administered questionnaire (see Appendix 8.0, page 75).
- ◆ Changes in ART, OI prophylaxis and other concomitant medication.
- ◆ For females of childbearing age allocated to the STI group, pregnancy tests will be performed one month before commencement of STI (see Flow Sheets, section 1.3, page 13).
- ◆ All women of childbearing age will be given continuing advice about avoiding pregnancy.
- ◆ If a woman becomes pregnant during the course of the trial, she will continue in the LCM or CMO arm like other patients, but if randomised in the STI arm, will ***NOT undergo*** a STI at any time during pregnancy or breast-feeding. Instead STIs would be deferred until after the baby has been weaned from breast-feeding. Advice on breast-feeding will be given according to national guidelines.
- ◆ Recording of compliance with the allocated management strategies on the follow-up form

At each 'drug collection' visit, the study nurse will:

- ◆ Administer the symptom check-list
- ◆ Assess adherence by questionnaire (see Appendix 8.0, page 75) and record numbers of returned pills
- ◆ Administer the next 4 weeks supply of drugs

If the study nurse has any clinical concerns at these visits, the patient should be referred to see a study doctor.

7.5 Management of patients allocated to the STI arm

More details of management for the STI arm have been developed after the pilot phase of STI (see Appendix 1.0, page 40). There are two issues to consider: first, when to shorten an STI; second, when not to recommence an STI during follow-up.

7.5.1 Timing of STIs

Among patients randomised to STIs, follow-up visits will be due 4 weeks before commencing a STI. Thus CD4 count results at weeks 48 will be available at the week 52 visit and, after review by the study doctor, the STI will commence from week 52 (see Flow

Sheets, section 1.3, page 13). For patients taking CBV+NVP, at each STI, CBV will be continued for 7 days after NVP is stopped.

7.5.2 Criteria for modifying the STI regimen and for restarting ART early

These include:

- ◆ CD4 cell count <50 cells/mm³, 8 weeks into STI (LCM only)
- ◆ Always restart for development of a new definitive WHO stage 4 diagnosis, or a definitive recurrence of a WHO stage 4 diagnosis (Appendix 5.0, page 67).
- ◆ Consider restart for development of a new or recurrent WHO stage 3 diagnosis or a new or recurrent presumptive WHO stage 4 diagnosis (Appendix 5.0, page 67).

If a patient develops clinical symptoms during a planned STI (detected at a nurse visit), then the nurse will refer the patient to be seen by the doctor. If the doctor assesses that the patient has a new or recurrent definitive WHO stage 4 event, ART should be restarted. If the doctor assesses that the patient has a new or recurrent WHO stage 3 event or a new or recurrent presumptive WHO stage 4 diagnosis, ART *may* be restarted but if the patient is in LCM, then blood will first be taken for CD4 cell count and the decision to restart therapy will also take account of the CD4 cell count result.

For patients restarting ART early during a planned STI, consideration will only be given to switching ART if symptoms persist, or CD4 count criteria (<50 cells/mm³) continue to be met (LCM only) at the next scheduled CD4 count after recommencing ART (see section 7.6.2, page 30).

Patients who undergo a shortened STI will be reconsidered for further STIs at the next scheduled STI start.

7.5.3 Deferring STI during follow-up

If a patient develops either of the following during the 12-week period of continuous ART, then STI should be deferred:

- ◆ CD4 count is <100 cells/mm³ after 8 weeks back on ART cycle (for those who are randomised to LCM)
- ◆ New or recurrent definitive WHO stage 4 disease (see Appendix 5.0, page 67) during the 12 week period on continuous ART (CMO or LCM) (see section 7.6.2, page 30 for switching guidelines).

In the event of either of the above, STI will be deferred until the next scheduled STI start (24 weeks) before reassessment for consideration of another STI (or consideration of switching ART regimen – see below).

An STI *may* also be deferred, at the discretion of the treating physician, for:

- ◆ New or recurrent WHO stage 3 disease or new or recurrent presumptive WHO stage 4 disease during the 12 week period on continuous ART (CMO or LCM)

7.6 Switching ART

7.6.1 Switching for Toxicity

Switching for severe clinical or laboratory toxicity will follow guidelines, based on clinical and laboratory grading of toxicities (Appendix 4.0, page 61). A symptom checklist will include questions on nausea/vomiting, rash, headache, fever, jaundice, abdominal pain etc. In the CMO arm, laboratory tests will be done (at 4 and 12 weeks and then 12-weekly) but results will **not be given back to clinicians** unless a laboratory grade 4 adverse event occurs. A system will be set up at each site (with standard operating procedures (SOPs)) for feedback of grade 4 results only to clinicians for patients in the CMO group. Clinicians caring for patients allocated to CMO may request laboratory tests if indicated by clinical symptoms, as in routine practice. For guidelines on switching of individual drugs for toxicity, see section 8.1.4, page 33.

7.6.2 Switching for failure of first-line therapy

Physicians will be **encouraged not to switch** ART before 48 weeks on continuous ART, or within 12 weeks after recommencing ART after a planned STI. Every attempt should be made to ensure that patients are adherent to ART before a switch of ART is considered.

After 48 weeks, switching therapy can be considered at any time for those on continuous ART, and after at least 8 weeks back on ART for those on STI arm.

Clinical criteria for consideration of switching therapy include:

- ◆ The development of a new WHO stage 4 diagnosis (see Appendix 5.0, page 67)

CD4 cell count criteria:

- ◆ CD4 cell count <50 cells/mm³ on 2 occasions, while on ART (for those randomised to STIs both at least 8 weeks after restarting ART). I.e. if a CD4 cell count is <50 cells/mm³ then it should be repeated as soon as practical and if still <50 cells/mm³, the patient should switch ART.

When a decision to change therapy has been taken, blood will be taken for haematology and biochemistry screens from all patients (CMO and LCM) to ensure there is no laboratory toxicity that would preclude the patient from taking the second-line therapy. A CD4 cell count will also be taken, but the result will not be returned to the clinician in the CMO arm, and a plasma specimen for future evaluation of HIV-RNA viral load and drug resistance will be collected.

After switching therapy, patients in the STI arm will be on continuous ART for at least 48 weeks (as at the start of the trial). CD4 counts will be made available to clinicians caring for patients in the CMO arm at the first scheduled lymphocyte subset count >48 weeks after switch (classified as ≤ 300 cells/mm³). If the CD4 cell count is ≥ 300 cells/mm³, the patient will recommence STI as during first-line therapy. If the CD4 cell count is <300 cells/mm³, then ART will continue.

7.7 Assessment of adherence

A study nurse will assess adherence at each 4-weekly visit by pill counts and a nurse administered adherence questionnaire (see Appendix 8.0, page 75).

7.8 Withdrawal from allocated strategy

Patients may voluntarily withdraw from the allocated trial treatment for any reason. If this occurs, the trial researchers are not under obligation to provide ART. The patient's withdrawal from the trial will not affect their access to the best standard of care within the national health system. Follow-up for documentation of any clinical endpoints should continue, if possible.

Clinical data, including weight, presence of signs or symptoms, and other concomitant medications should be recorded at the time of withdrawal. In addition, a blood sample for plasma storage should be taken for storage (for subsequent viral load and possible resistance testing). Blood should also be taken for FBC, biochemistry and T-cell subsets (not returned to clinicians of patients in the CMO arm).

If a patient has an unscheduled period off treatment or not in follow-up, this should be fully recorded on follow-up forms.

7.9 Recording and reporting of Adverse Events, Death, HIV progression and protocol violations

If the patient has died, experienced any new or recurrent WHO stage 4 illness or experienced an adverse event (serious, Grade 3 or 4, or one leading to a modification of ART) since the last visit, the investigator/study co-ordinator will complete specific case report forms.

If there is any violation of the protocol for any reason, this should be fully recorded.

7.9.1 Serious Adverse Events (SAE):

According to the ICH Harmonised Tripartite Guidelines for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (1994), a Serious Adverse Event (SAE) is defined as 'any untoward medical occurrence' that:

1. **results in death**
2. **is life-threatening** (patient was actually at risk of death at the time of the event)
3. **requires unplanned inpatient hospitalisation or prolongation of existing hospitalisation**
4. **results in persistent or significant disability/incapacity** or is a congenital anomaly/birth defect
5. any **other important medical condition, which, though not included in the above,** may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed (e.g. intensive treatment in hospital or at home for allergic bronchospasm; blood dyscrasia or convulsions that do not result in hospitalisation, or the development of drug dependency)

In the context of the DART trial SAEs need only be reported if considered **not** HIV-related **only**. All such SAEs must be recorded on the Serious Adverse Event form and reported to the MRC CTU as soon as possible after the event.

The MRC CTU will report SAEs that are definitely or probably related to antiretrovirals to the relevant pharmaceutical companies and/or to the regulatory authorities in timely fashion, as appropriate.

National requirements for reporting of SAEs will be followed.

Data on SAEs will be tabulated and presented to the Data and Safety Monitoring Committee (DSMC; see section 9.4, page 35).

Other grade 3 and 4 adverse events (see Appendix 4.0, page 61) should be reported on the next scheduled follow-up.

8.0 Drug Regimens

8.1 Antiretroviral Therapy

Table 5 First and second-line drug regimens for DART (For details see Appendix 3.0, page 57)

Patient numbers	First-line treatment	Second-line treatment
2100	combivir plus TDF	2NRTIs plus boosted PI* or NVP
600	combivir plus ABC/NVP (blinded substudy)	2NRTIs plus TDF** or boosted PI*
300	combivir plus NVP	2NRTIs plus boosted PI* or TDF**

* boosted PI should be for patients with new WHO stage 4 diagnosis (those switching for progression to WHO stage 3 disease may receive NVP if they were on TDF for first-line or TDF if they were on NVP). The boosted PI will most probably be Saquinavir/Ritonavir or Lopinavir/ Ritonavir

** TDF should be given as second-line to patients also on anti-tuberculosis therapy

8.1.1 First-line antiretroviral drugs

All patients will receive a triple combination of ART throughout the trial. All patients will receive combivir as part of their first-line regimen. The third drug for 600 patients enrolled in the NORA substudy will be blinded ABC or NVP plus placebo (see Appendix 2.0, page 43). For all patients not enrolled in the substudy TDF and NVP will be available as the third first-line drug for patients. Patients with any absolute (e.g. on concomitant anti-tuberculosis therapy) or relative (e.g. receipt of previous NVP in pregnancy) contra-indications to receipt of NVP, should receive TDF as the third drug.

TDF and NVP will be allocated equally between Zimbabwe and Uganda. It is expected that patients will stay for about 2.5 years on each regimen. Upon failure of a second-line regimen, the best possible combination will be selected from first and second-line drugs for the remaining duration of the trial. After trial completion follow-up healthcare will be provided by the national health systems (see Appendix 9.0, page 76, and letters from the Ministries of Health).

8.1.2 Second-line antiretroviral drugs

Second-line therapy will be 2NRTIs + TDF or 2NRTIs + NVP or 2NRTIs + a boosted PI. The choice of second-line will be determined by whether the patient is also on anti-tuberculosis therapy, the first-line ART already received, the WHO disease stage and CD4 count (LCM arm only) at the time of switch (see Table 5 above). For those patients who have received NVP as first-line therapy, TDF will also be available as an option for second-line therapy, should there be particular contra-indications to use of a PI.

8.1.3 Provision of trial drugs

Patients will be provided with a 4-weekly supply of drugs throughout the trial. Patients will be requested to return all empty bottles and to bring any bottles in use to the follow-up clinic.

On no account should any drug assigned to one patient be used by another patient. Unused drug must be returned to the site if a patient withdraws from treatment.

All drug dispensed and returned to the site should be documented on a treatment log for each patient. At each site, a named person (trial pharmacist or research nurse) will be required to maintain complete records of all study medication dispensed. The procedures to be followed will adhere to the Good Clinical Practices (GCP) guidelines on drug accountability. MRC CTU will monitor drug accountability at site visits.

8.1.4 Modification of therapy for toxicity

For reactions where the cause may be attributed to one or more trial drugs, all drugs should be stopped temporarily and may be restarted if the symptoms resolve and this is appropriate. If the symptoms are intolerable or do not resolve, an alternative drug **of the same class** may be substituted if this is considered appropriate by the investigator (see Table 6 below) and other drugs restarted. ZDV and 3TC will be available as separate drugs for patients who need to stop one drug for toxicity. See also Appendix 4.0, page 61.

Table 6 Guidelines for Switching for Toxicity

Event	Switch
ZDV toxicity	Substitute ZDV with d4T (replace combivir with d4T + 3TC)
3TC toxicity	Substitute 3TC with ddI (replace combivir with ZDV + ddI)
NVP toxicity	Substitute NVP with TDF
ABC toxicity	Substitute ABC with NVP or TDF

TDF toxicity	Substitute TDF with NVP
ddI toxicity	likely to be 3TC (individual judgement)
d4T toxicity	likely to be ZDV (individual judgement)
PI	NVP or TDF (depending on which has not previously been used)

8.2 Prophylaxis against Opportunistic Infections

Decisions on prophylaxis strategies will be made taking into account National guidelines. All prophylaxis therapy should be recorded on forms.

8.3 Medications not permitted/ Precautions

Patients should not be co-enrolled in other ART trials or receive ART outside the trial. Patients will be encouraged to seek advice prior to taking any other medication. See Appendix 3.0, page 57 for details of drug interactions.

8.4 Data on concomitant medications

At each visit, information on other medications, including start dates, and reason(s) for taking should be documented on follow-up forms.

9.0 Management of the Trial

9.1 Trial Steering Committee

The trial will be managed by a Trial Steering Committee (TSC) with an independent chairperson (Professor Ian Weller), independent members and one Principal Investigator or key investigator from each site and from the MRC CTU and Imperial College.

A subgroup of the TSC will undertake monitoring of the STI pilot data, see Appendix 1.0, page 40.

In addition to the above, a subcommittee of the TSC will be formed to undertake close monitoring of CD4 cell counts on a monthly basis among patients in the CMO and STI arms of the study (after completion of the STI pilot). The reason for this is to ensure that asymptomatic patients with very low CD4 cell counts are not continuing on STIs and therefore being at high risk of developing clinical progression. Should this occur, the subcommittee could convene a meeting of the DSMC to consider its findings and would advise the Trial Steering Committee about appropriate action, e.g. change of trial design to shorten the period of STIs.

9.2 Trial Management Groups

An International Co-ordinating Group (ICG) of principal and key investigators from each site, as well as members from MRC CTU will communicate regularly to ensure that the trial is proceeding well across all 3 sites. Local Trial Management Committees (LTMCs) composed of investigators at each site will meet regularly. There will be regular teleconferences to ensure good communication across sites and with MRC CTU and Imperial College.

9.3 Data Management and Monitoring

An Analysis and Data Management Committee will be set up with data management, computing and statistician members from each site and the MRC-CTU, chaired by the Trial Statistician. This Committee will be responsible for setting up the databases at each site and for co-ordination of timely merging of data from each site at MRC CTU, where the central database will be held. The committee will be responsible for ensuring that the system for data collection is working consistently across the sites, for developing the trial analysis plan and 'shell' tables to be provided to the DSMC, and for making decisions about analyses.

Each site will be responsible for maintaining its own database and for timely transfer of checked data to the MRC CTU for merging of data with those from the other sites. Staff from MRC CTU will visit clinical sites to validate and monitor data and this may also be done across sites (e.g. a data manager from Zimbabwe may visit Uganda), under the oversight of the Analysis and Data Management Committee. The clinical investigators and participants, by giving consent, agree that within the host country's Data Protection Law, the MRC CTU may consult and /or copy source records (clinical notes, laboratory values) in order to do this. Such information will be treated as strictly confidential and will in no circumstances be made publicly available. The monitoring will adhere to MRC Good Clinical Practice guidelines (based on ICH guidelines). The following data should be verifiable from source documents: signed consent forms; dates of visits including laboratory results; eligibility and baseline values for all patients; all clinical endpoints; all serious/severe adverse events; an ongoing random 10% sample of routine patient clinical and laboratory data; drug compliance; dates drug dispensed and (if necessary) drugs returned; pharmacy/clinic drug logs; concomitant medication.

9.4 Data and Safety Monitoring Committee (DSMC)

An independent Data and Safety Monitoring Committee (DSMC) will be established and will monitor all aspects of the trial including the NORA substudy (see Appendix 2.0, page 43). The DSMC will consider findings from any other relevant studies and review trial data on recruitment, safety, adherence to randomised strategies and efficacy, in strict confidence approximately every 6 months. The DSMC will report to the DART Trial Steering Committee and to the Ethics Committee in each country, if in their view the data provide proof beyond reasonable doubt that one of the allocated strategies is better than its comparator in terms of a difference of clinically significant magnitude in a primary outcome. The guiding statistical criteria for "proof beyond reasonable doubt" is a Haybittle-Peto type rule based on the 99.9% confidence interval of the relative hazard of disease progression in each interim analysis. The DART Trial Steering Committee will then decide whether to amend or stop the trial before the end of the planned follow-up. In addition, the DSMC will

meet with the DART Trial Steering Committee to consider results from the STI pilot study. The decision whether to go ahead with the evaluation of the planned STI strategy or an amended strategy will be taken jointly by the two committees in that meeting. The MRC CTU will undertake the organisation of the DSMC meetings.

9.5 Endpoint Review Committee

An Endpoint Review Committee will be appointed whose remit will be to determine the validity of potential endpoints that do not clearly satisfy the standard criteria, as defined by the protocol. It will have an independent Chair and will include Project Leaders from each site as well as other clinicians. No member will review endpoints from their own site. Terms of reference for the Endpoint Review Committee will be drawn up.

10.0 Statistics

10.1 Sample Size

The aim is to recruit 3000 patients (1000 from each of the 3 sites – 2 in Uganda, 1 in Zimbabwe) during the first year. Patients will be allocated in a 1:1 ratio to LCM or CMO. Data from several studies co-ordinated by the MRC Clinical Trials Unit (CTU) in the UK in adults show that among patients starting triple ART with CD4 counts <50, 50-99, 100-199, the proportions with CD4 >200 cells/mm³ are 20%, 43%, 73% respectively at 6 months after starting ART and 33%; 68%, 77% respectively at 12 months. Thus if the proportions of patients with CD4 counts in these three ranges are equal, we would expect 60% of patients to have CD4 ≥ 200 cells/mm³ and to qualify for the second randomisation to STI or no STI, based on a threshold of 200 cells/mm³ (n=1800).

The estimation of the sample size is based on the following assumptions:

1. Progression rate to a new stage 4 disease or death is 15% per year in the LCM arm. This is based on data from the Entebbe cohort which suggest that the cumulative proportion of untreated patients with CD4 count less than 200 cells/mm³ progressing to WHO stage 4 or death is 0.55, equivalent to a progression rate of 80% per year. A progression rate of 15% per year therefore represents a reduction of more than 80% under ART.
2. Progression rate to a new stage 4 disease or death in patients eligible for the second randomisation on continuous ART is 10% per year (this is lower than the overall progression rate as these patients have achieved CD4 cell counts >200 cells/mm³).
3. Recruitment is over 1 year and follow-up for a further 4 years. For the second randomisation recruitment is over 2 years and follow-up for at least 3 years.
4. Loss to follow-up rate 3.3% per year, equivalent to approximately 15% cumulative proportion of patients lost to follow-up by 5 years.
5. Type I error probability (alpha) 0.05 (two sided)
6. A progression rate of up to 17.5% per year in the CMO arm would be considered 'equivalent' to that in LCM (15%).

7. A progression rate of up to 13% per year in the STI arm would be considered 'equivalent' to that in the no STI arm (10%).
8. Power 80% to detect equivalence of LCM and CMO, i.e. the upper limit of the 95% confidence interval of the hazard ratio (CMO relative to LCM) will be no greater than 1.17 (a relative increase of 17%, equivalent to an annual rate of progression of 17.5% in the CMO arm compared to 15% in the LCM arm) with probability 0.80 if CMO and LCM were truly equivalent.
9. Power 80% to detect equivalence of STI and no STI, i.e. the upper limit of the 95% confidence interval of the hazard ratio (STI relative to no STI) will be no greater than 1.3 (a relative increase of 30%, equivalent to an annual rate of progression of 13% in the STI arm compared to 10% in the no STI arm) with probability 0.80 if STI and no STI were truly equivalent.

Under these assumptions, a total of 2862 would be required for the LCM versus CMO comparison and 1520 for the STI versus no STI comparison. The target number of events (progression to a new stage 4 event or death) is 1392 for the LCM versus CMO comparison and 501 for the STI versus no STI comparison. An additional 100 patients would be required for the STI pilot study.

Assuming that recruitment into the LCM versus CMO comparison takes place through the first two years rather than one year, a total of 3101 patients (rather than 2862) would be required for the LCM versus CMO comparison.

Assuming the STI versus CT randomisation is based on a threshold of 300 CD4 cells/mm³ rather than 200 cells/mm³, thus in DART so far we would expect around 20% of patients to be eligible for the second randomisation at 48 weeks. Excluding those already included in the STI pilot this would leave at least 600 patients eligible for the second randomisation.

Assuming:

10. A progression rate of up to 16% per year in the STI arm would be considered 'equivalent' to that in the no STI arm (10%).
11. Power 80% to detect equivalence of STI and no STI, i.e. the upper limit of the 95% confidence interval of the hazard ratio (STI relative to no STI) will be no greater than 1.6 (a relative increase of 60%, equivalent to an annual rate of progression of 16% in the STI arm compared to 10% in the no STI arm) with probability 0.80 if STI and no STI were truly equivalent.

Then 556 patients would be required for the STI versus no STI comparison (target number of events 159).

10.2 Analysis Plan

The primary analysis will compare LCM with CMO and STI with no STI as allocated (intention to treat (ITT)) in terms of:

- a) Progression to a new HIV stage 4 event or death and
- b) Drug-related grade 4 serious adverse events

Time-to-event methods (Kaplan-Meier plots, stratified log rank test and Cox proportional hazard regression) will be used for these comparisons. The frequency of grade 4 adverse events will be tabulated by body systems and randomised group and the groups will be

compared using the X^2 test. Wilcoxon's rank-sum test will be used to compare median CD4 cell counts at 3 years in the different allocated strategies.

11.0 Regulatory/ Ethics Approval

This document, along with any subsequent modifications and with the sample informed consent documents will be reviewed by the Ethics Committee from each participating site as well as by Ethics Committees in the UK (Liverpool School of Tropical Medicine and Imperial College).

Regulatory approval for conduct of the trial and use of antiretrovirals in the trial will be obtained.

12.0 Confidentiality

A unique trial number will identify all laboratory specimens, case record forms, and other records and no names will be used, in order to maintain confidentiality. All records will be kept in locked locations. Clinical information will not be released without written permission, except as necessary for monitoring by the trial monitors.

13.0 Publication

The ICG will develop guidelines for the preparation of papers (including abstracts) for presentation at national and international meetings, as well as the preparation of manuscripts for peer-reviewed publication. Any publication or presentation during the active phase of the study must have prior approval of the TSC. The TSC will define the strategy for, and resolve any problems of authorship and maintain the quality of publications. All publications will acknowledge appropriate funding sources. The DART TSC is the custodian of the data and specimens generated from the DART trial; DART trial data are not the property of individual participating investigators or health care facilities where the data were generated.

14.0 References

1. Altfeld M, Rosenberg ES, Walker BD. Cellular Immune Responses and Viral Diversity in Individuals Treated during Acute and Early HIV-1 Infection. *J. Exp. Med.* 2001 193: 169-180.
2. Lori I, Maserati R, Folli A et al. Structured treatment interruptions to control HIV-1 infection. *Lancet* 2000, 354, 287.
3. Lisziewicz J, Rosenberg E, Lieberman J et al. Control of HIV despite the discontinuation of antiretroviral therapy. *N Engl J Med*, 1999, 340, 1683.
4. Rosenberg ES, Altfeld M, Poon SH, et al. Immune control of HIV-1 after early treatment of acute infection. *Nature* 2000, 407: 523-526.
5. Amie C et al. Treatment interruptions in heavily antiretroviral pre-treated patients: clinical and genotypic evolution. *First International AIDS Society Conference on HIV Pathogenesis and Treatment*, Buenos Aires, abstract 445, 2001.
6. Deeks SG, Wrin T, Liegler T, Hoh R, Hayden M, Barbour JD, Hellmann N, Petropoulos CJ, McCune JM, Hellerstein MK, Grant RM. Virologic and

Immunologic Consequences of Discontinuing Combination Antiretroviral-Drug Therapy in HIV-Infected Patients with Detectable Viremia. *N Eng J Med*, Feb 2001; 344:472-480.

7. Ruiz L, Martinez-Picardo J, Romeu J, Paredes R, Khalil Zayat M, Marfil S, Negro E, Sirera G, Tural C and Clotet B. Structured treatment interruption in chronically HIV-1 infected patients after long-term viral suppression. *AIDS* 2000, 14: 397-403
8. Wallace M et al. Structured treatment interruption: effect on triglyceride levels. *First International AIDS Society Conference on HIV Pathogenesis and Treatment*, Buenos Aires, abstract 448, 2001.
9. Youle M, Janossy G, Turnbull W, Tilling R, Loveday C, Mocroft A, Tyrer M, Madge S, Wilson D, Dykhoff A, Johnson M, Phillips A, for the Royal Free Centre for HIV Medicine. Changes in CD4 lymphocyte counts after interruption of therapy in patients with viral failure on protease inhibitor-containing regimens *AIDS* 2000, 14(12): 1717-20
10. Scaling up antiretroviral therapy in resource limited settings: guidelines for a public health approach. 2002. http://www.who.int/hiv/pub/prev_care/en/ScalingUp_E.pdf ISBN 92 4 154570 4
11. Schooley RT, Ruane P, Myers RA et al for the Study 902 Team. TDF DF in antiretroviral-experience patients: results from a 48-week, randomised, double-blind study. *AIDS* 2002, 16: 1257-1263.

Appendix 1.0 Structured Treatment Interruptions (STI) Pilot Study

A pilot study will be undertaken to provide preliminary data on the safety of STI in this patient population in whom antiretroviral therapy is started at a relatively late stage of HIV disease. Therefore, *before commencing the second randomisation to either structured treatment interruption (STI) or to continuous ART (no STI)*, the first 100 patients (from either the CMO arm or the LCM arm, at any of the three study sites) with CD4 cell counts ≥ 200 cells/mm³ at week 24 will be enrolled into a non-randomised pilot study and undergo a treatment interruption of 12 weeks, followed by restarting therapy for 12 weeks.

1.1 Monitoring of individual patients

During this 24-week period the patients will be seen by the doctor every 4 weeks and 4-weekly CD4 cell counts will be performed on all 100 patients and reported to the clinicians in the LCM arm. For CMO patients in the STI pilot the Trial Manager at each site will check all CD4 counts while on STI and if any are < 50 cells/mm³ they will report the result to the clinic as < 50 cells/mm³). These 100 patients will subsequently be excluded from the analysis of the STI versus continuous ART randomisation, **but not from the CMO versus LCM randomisation**. At the end of the 24 weeks, patients will remain in their original LCM/CMO arm and will continue with STIs. Patients will continue to receive drugs and follow-up as in the main DART study.

1.2 Monitoring of the group data

Two members of the TSC who are not involved with clinical management of DART patients will look at individual CD4 counts for all patients enrolled in the STI pilot after each 2-weekly data merge, **without** knowledge of CMO/LCM allocation.

The data will be summarised by CD4 at baseline (before ART) and before the STI, to describe the following:

- the rate of decline of CD4
- the proportion with new stage 3 or 4 WHO events,
- the proportion of patients with CD4 < 50 cells/mm³
- the proportion with a reduction in CD4 of 150 cells/mm³ or greater from the start of the STI.

If the rate of decline were considered too fast (given baseline and pre-STI values) by the 2 TSC members, or if, for example, $> 10\%$ patients in the STI experienced any of the above outcomes, this would be further discussed with the chair of the TSC. They could decide whether they need to inform the DSMC and TSC immediately, prompting a full analysis of all data accrued in the STI pilot to this point in time in the STI pilot for urgent consideration by the DSMC.

After the 100th patient has been enrolled and completed 12 weeks STI, the data will immediately be analysed and considered jointly by the Trial Steering Committee and the DSMC, to determine whether it is safe to start the second randomisation (STI or continuous

ART). The Committees may be satisfied about the safety of STI either after reviewing data on 12 weeks of STI on all 100 patients, or they may recommend waiting until the results of the effect on CD4 count of restarting ART for a further 12 weeks after the STI are available on all 100 patients before making a decision about commencing the second randomisation.

1.3 Guidelines for management during STI pilot.

1. If CD4 count falls to <50 cells/mm³, repeat within 2 weeks, and if still <50 cells/mm³, then the patient should be restarted on ART for LCM arm
2. Clinical criteria (see Appendix 5.0, page 67) for restarting ART during a STI would include for LCM and CMO arms:
 - ◆ the development of a new WHO stage 3 or 4 diagnosis

(NB. if CD4 cell count is not low (e.g. >150 cells/mm³), despite the presence of symptoms consistent with stage 3 or 4 disease, the clinician may decide to continue STI, and repeat CD4 cell count in 4 weeks. If by then the CD4 count has declined or if symptoms do not resolve, ART should be restarted.

1.4 Guidelines for the DSMC and Steering Committees.

If any of the following occurred during the pilot STI study, this would be of concern to the TSC and DSMC and would suggest that a revision of the STI trial design would be necessary:

1. If a significant number of patients (e.g. $>10\%$) develop the following during an STI:
 - a. Progression to new stage 3 or stage 4 event
 - b. CD4 count <50 cell/mm³
 - c. Reduction in CD4 cell count of 150 cells or more from the value at the start of the STI
2. Analyses would be undertaken to explore the relationship between development of the above and baseline characteristics, including baseline CD4 cell count. The committees may recommend a change to the trial design, depending on the group of patients in whom this occurs. For example, they could recommend:
 - a. Only enrol those with CD4 cell counts above 100 cells/mm³ at baseline into the trial
 - b. Shorten the period of STI e.g. 12 weeks on and 8 weeks off ART
 - c. In any event, they may recommend continuation of the pilot study with the new design.

1.5 Flow Sheet for STI pilot

Table 7 STI Pilot for 100 patients (completed 24 weeks in CMO or LCM and with CD4 cell counts at week 24 of 200 cells/mm³ or higher.

EVENTS	WEEK of STI pilot study						
	Start of STI			Restart ART			Restart STI
	0 (Week 28 in trial)	4 (32)	8 (36)	12 (40)	16 (44)	20 (48)	24 (52)
History & Physical ¹	X	X	X	X	X	X	X
Symptom check list	X	X	X	X	X	X	X
Pregnancy Test ²	X					X	
Haematology ³	X	X	X	X	X	X	X
Biochemistry ⁴	X		X	X		X	X
Lymphocyte Subsets ⁵	X	X	X	X	X	X	X
Plasma storage ⁶ + DNA pellet	X	X	X	X	X	X	X
Adherence assessment ⁷	X				X	X	X

¹ Clinical: including weight, WHO staging for HIV. Doctor sees patient at every visit.

² If positive, exclude from STI pilot study.

³ Haematology: Hb, MCV, WBC, Lymphocytes, Neutrophils, and Platelets.

⁴ Biochemistry: Blood Urea Nitrogen or Creatinine, AST or ALT, Bilirubin, – results to be given back for all patients in the pilot.

⁵ CD4, CD8, CD3, percentage and total lymphocyte count.

⁶ Take 6 ml blood into EDTA. Store DNA pellet (if feasible) See Appendix 7.0, page 74 for instructions about storage.

⁷ Take plasma at the time of change to second-line regimen (and DNA pellet if feasible).

See Appendix 8.0, page 75.

Appendix 2.0 Nevirapine OR Abacavir (NORA) Substudy

A randomised, double-blind, phase II (substudy) trial to evaluate the toxicity of Abacavir compared with Nevirapine, both in combination with ZDV+3TC (combivir), as first-line antiretroviral therapy in patients participating in the DART trial

2.1 Objective

To assess the safety of abacavir (ABC) compared with nevirapine (NVP), (both in combination with ZDV+3TC (combivir)) in African patients.

2.2 Background and Rationale

2.2.1 Hypersensitivity reaction to Abacavir

In clinical studies, approximately 3-5% of patients receiving ABC develop a hypersensitivity reaction. This is characterised by symptoms which usually appear within the first six weeks of initiation of treatment with ABC (median time to onset is 11 days) and most often include fever, rash, gastrointestinal symptoms (nausea, vomiting, diarrhoea, or abdominal pain), and lethargy or malaise. Other signs and symptoms may include respiratory symptoms (dyspnoea, sore throat, cough), musculoskeletal symptoms (myalgia, rarely myolysis, arthralgia), headache, paraesthesiae and oedema. Some patients with hypersensitivity reactions were initially thought to have respiratory disease (pneumonia, bronchitis, pharyngitis) or a flu-like illness.

The rash is variable and may be absent, but often appears maculopapular or urticarial. Laboratory abnormalities that may accompany ABC hypersensitivity include abnormal liver function tests or elevated creatinine phosphokinase or creatinine or lymphopenia.

Symptoms related to the hypersensitivity reaction worsen with continued therapy but usually resolve upon discontinuation of ABC. Restarting ABC following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence of the hypersensitivity reaction may be more severe than on initial presentation and may include life-threatening hypotension and death. Subjects who develop a hypersensitivity reaction must not be re-challenged with ABC.

As ABC hypersensitivity is heralded by the onset of relatively vague symptoms and signs, it could be mistaken for an acute intercurrent infection (e.g. malaria or flu), or be confused with immune reconstitution disease. Standard practice in the West (where rates of intercurrent infection are much lower, and there is likely to be less endemic sub-clinical infection to precipitate immune reconstitution disease), is to stop ABC for symptoms consistent with hypersensitivity and not to restart the drug. High rates of possible reactions that cannot be delineated further clinically could render ABC difficult to use in Africa, or substantially reduce its role. However, it is possible that even if ABC is difficult to use as first-line therapy because of difficulties distinguishing hypersensitivity from immune reconstitution disease, it might be possible to use it sometime after 3 or more months into ARV treatment when the risk of immune reconstitution (IR) disease is lower. Reasons for doing this might include the desire to switch to a simpler regimen (ABC is available in combination with ZDV and 3TC as a single formulation, taken as 1 tablet twice daily) or the need to start antituberculosis

therapy. It could also be useful in a second-line regimen. No study has been carried out to address these questions and no data are available.

2.2.2 Adverse reactions to NVP

Signs and symptoms of NVP reaction include rash with or without fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, and/or hepatitis, eosinophilia, granulocytopenia, and renal dysfunction.

The most common clinical toxicity of NVP is rash, which occurred in 15-20% of subjects in phase I/II trials. Severe and life-threatening skin reactions, including fatal cases, have occurred in 2-5% subjects treated with NVP. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterised by rash, constitutional findings and organ dysfunction.

Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. The majority of rashes occur within the first 6 weeks of therapy, and severe rashes occur earlier, usually within the first 28 days of treatment; 25% of the patients with severe rashes required hospitalisation. Overall, 7% of patients in clinical trials discontinued NVP due to rash.

In one clinical trial, concomitant use of prednisone to prevent NVP-associated rash increased the incidence and severity of rash during the first 6 weeks of NVP therapy. The use of prednisone to prevent NVP-associated rash is not recommended.

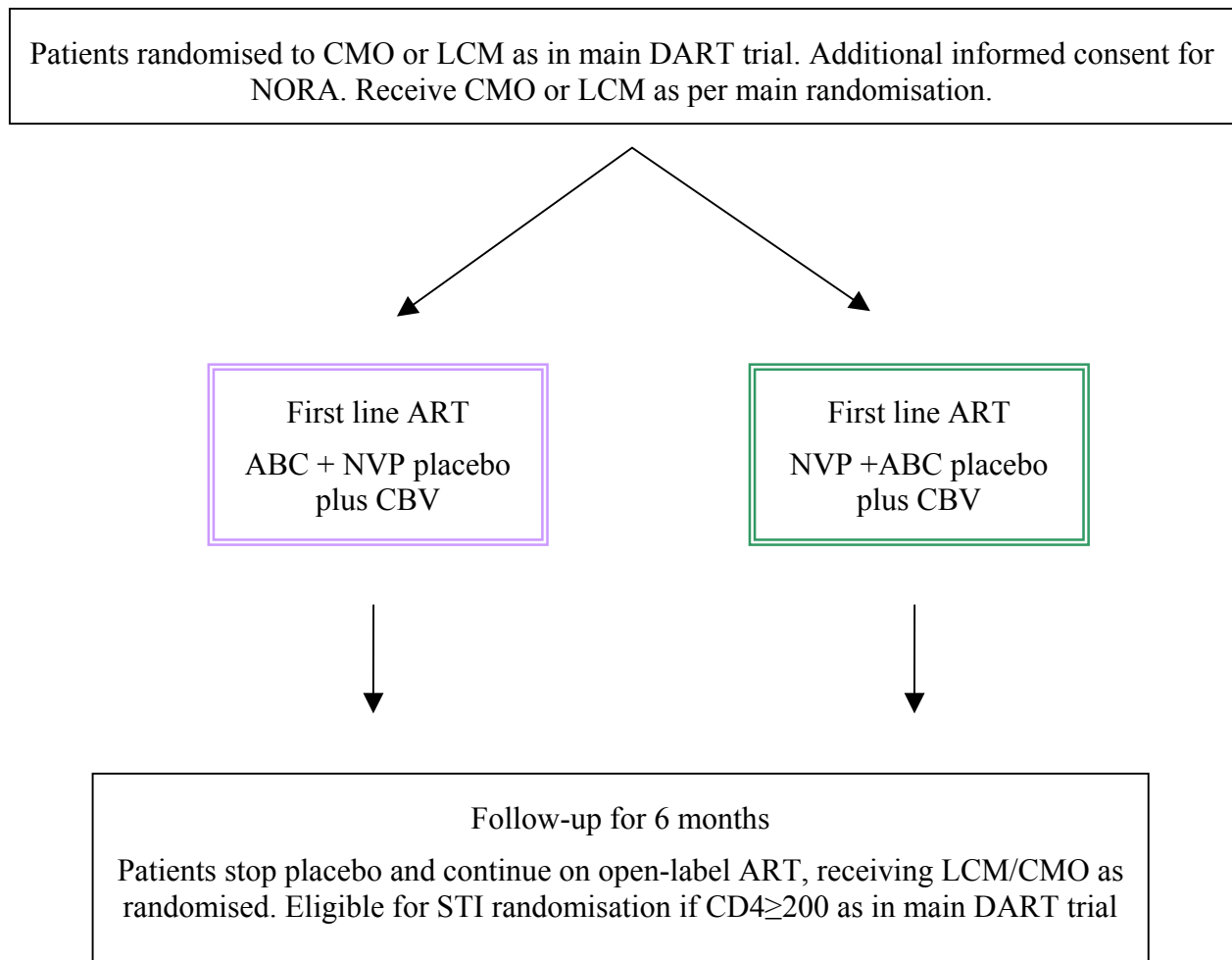
Elevation of liver enzyme levels frequently occurs during drug therapy with NVP. Hepatitis and cases of fatal hepatic toxicity have been reported but are rare.

2.3 Trial Design

It is proposed to undertake this substudy in 600 patients enrolled in the DART trial. Separate consent will be sought for the substudy. Patients will be randomised to ABC (plus NVP placebo) or NVP plus ABC placebo in a 1:1 ratio, stratified by allocation to CMO/LCM arms. The blinded part of the trial will take place over 6 months, during which no patients will undergo STIs.

The trial sites will be in Entebbe, Uganda and JCRC, Kampala, Uganda. These are 2 of the 3 sites for the DART trial.

2.4 NORA Trial Schema



2.5 Endpoints

2.5.1 Primary endpoint:

- Any serious adverse event that is definitely/probably or uncertainly related to blinded trial drugs (blinded ABC or blinded NVP) where the adverse event occurs while on ART or within 30 days of receiving ART. A SAE in the context of the DART trial is defined as any untoward medical occurrence that is not definitely HIV related only and either:
 - results in death
 - is life-threatening (patient was actually at risk of death at the time of the event)
 - requires unplanned inpatient hospitalisation or prolongation of existing hospitalisation
 - results in persistent or significant disability/incapacity
 - is any other important medical events considered serious by the investigator (e.g. intensive treatment in an emergency room or at home)

for allergic bronchospasm; blood dyscrasia or convulsions that do not result in hospitalisation)

All suspected hypersensitivity reactions must be reported as a SAE, these should be categorized as “other important medical conditions” unless they fall into one of the more specific categories.

2.5.2 Secondary Endpoints

- Adverse events of any grade leading to permanent stopping of trial drug:
- Fever, rash or raised liver enzymes (blinded in CMO except grade 4) leading to discontinuation of trial drug.
- Grade 4 events irrespective of whether they result in stopping trial drug

Adverse events will be classified by whether they are definitely/probably related, uncertainly related or unrelated/unlikely to be related to trial drug.

2.6 NORA Criteria for Inclusion/Exclusion

2.6.1 Inclusion Criteria

1. Documentation of HIV-1 infection: antibody positive serology by ELISA test (confirmed by licensed second ELISA or Western Blot)
2. Age > 18 years
3. Symptomatic WHO stage 2, 3 or 4 HIV disease and CD4 < 200 cells/mm³
4. ART naïve (except for ART use during pregnancy for the prevention of mother-to-child HIV transmission)
5. Agreement and documented informed consent to participate in DART main study and willingness to be randomised to ABC or NVP, if eligible
6. Life expectancy of at least 3 months

2.6.2 Exclusion criteria

1. Cannot or unlikely to attend regularly (e.g. usual residence too far from Study Centre)
2. Likelihood of poor compliance
3. Presence of acute infection (e.g. malaria, acute hepatitis, pneumococcal pneumonia, non-typhoid salmonella septicaemia, cryptococcal meningitis, acute hepatitis). Patients may be admitted after recovery of an acute infection. Patients with tuberculosis (TB) will not be enrolled while on the intensive phase of anti-tuberculosis therapy, but should be re-evaluated after the intensive phase and a decision made then about starting ART. Patients starting ART whilst on anti-tuberculosis therapy after the intensive phase will not receive NVP, nor will they be randomised into the NORA substudy.
4. On chemotherapy for malignancy
5. Laboratory abnormalities which are a contra-indication for the patient to start ART (e.g. Haemoglobin <8g/dl, neutrophils <0.50x10⁹/l, AST or ALT >5 x the upper limit of normal (ULN), grade 3 renal dysfunction - creatinine >360 µmol/l and /or urea >5 x ULN).
6. Pregnancy or breast-feeding

7. Family/household members already enrolled in NORA

Patients included in this substudy should not be included in the STI pilot substudy

2.7 Sample size

Data from a cohort of 70 patients on ddi/d4T/NVP, over an average follow-up of 6 months; suggest a cumulative proportion of 15% of patients experiencing an SAE during the first 24 weeks (unpublished data from Cascade). 300 patients per arm will be sufficient to detect a difference between 15% in one arm and 8% in the other arm with power 80% using a two-sided chi-square test of difference in proportions with $\alpha = 0.05$.

The substudy will last for 6 months. After that patients will switch to unblinded drug and will remain on the monitoring arm they were randomised to before the substudy and will become eligible for the STI randomisation, providing their CD4 count is 200cells/mm³ or higher. Drug supply, patient management and follow-up will continue as in the main DART study.

2.8 Analysis Plan

The frequency of SAEs, all grade 4 adverse events and all adverse events leading to discontinuation of trial drug will be tabulated by body systems and the two randomised groups will be compared in terms of the proportion of patients experiencing any of the primary and secondary outcomes of the substudy by week 24, using the X^2 test, stratified by allocation to CLM or CMO. Kaplan-Meier plots and log-rank test will be used to compare the two groups in terms of time to first SAE.

2.9 Management of Adverse reactions

All patients will be followed up as in the main DART trial and given advice about reactions to ZDV, 3TC and NVP. They will also be given standard advice and warnings about possible reactions to ABC.

2.9.1 Management of reactions to combivir

Patients developing adverse reactions that can reasonably be attributed to CBV (e.g. anaemia or neutropenia as reaction to ZDV) may switch the responsible drug to an alternative as in the main part DART trial (e.g. ZDV to d4T). In such a case there would be no need for unblinding and the appropriate CRFs should be completed as in the main part of the trial.

2.9.2 Management of reactions to blinded drug

Patients will be instructed to seek advice from the clinic within 12-24 hours if they develop any of the following symptoms: fever, rash, gastrointestinal symptoms (nausea, vomiting, diarrhoea, or abdominal pain), fatigue, lethargy, malaise, respiratory symptoms (dyspnoea, sore throat, cough), musculoskeletal symptoms (myalgia, myolysis, arthralgia), headache, paraesthesia, oedema, oral lesions, conjunctivitis, blisters, general ill feeling or “flu-like”

symptoms, dark urine, tiredness, pale stools, pain, ache, or sensitivity to touch on the right side below the ribs, lack of appetite, yellowing skin or whites of the eyes.

On attending the clinic they should be assessed clinically with the standard symptom checklist and examination and CRFs completed as appropriate. In the CMO arm, results of scheduled laboratory tests can be requested if indicated by symptoms; documented approval for this should be obtained from the Project Leader as in the main DART trial. As with standard management of adverse reactions, if a reaction is felt to be possible but other causes have not been excluded, the patient may be maintained on treatment under close observation. However, if, after investigations and discussion with the Project Leader, the clinical event is considered a potential reaction to ABC or NVP, it is likely that unblinding will be necessary for patient management (after completion of SAE and Hypersensitivity CRFs). This would avoid the possibility of restarting ABC or NVP in a patient who is experiencing a drug-related reaction. It will also facilitate allowing for the long half-life of NVP when stopping drugs.

2.9.3 Management of nevirapine reactions

NVP should be discontinued and not restarted if patients experience hypersensitivity characterized by rash with constitutional symptoms (such as fever, blistering, oral lesions, conjunctivitis, swelling, muscles or joint aches or general malaise) plus visceral involvement such as hepatitis, eosinophilia, granulocytopenia and renal dysfunction.

Patients experiencing mild to moderate rash without constitutional symptoms or visceral involvement during the 14-day lead-in period of 200 mg/day should not have their NVP dose increased until the rash has resolved.

If stopping NVP, if the patient is well enough to tolerate any drugs, CBV should be continued and TDF added as soon as possible. Note that if the reaction is mild it may be possible to start with TDF immediately. If necessary, all drugs should be stopped and CBV/TDF started soon after toxicity symptoms resolve.

2.9.4 Management of abacavir reactions

If, on unblinding, a patient is found to have experienced a reaction to ABC, ABC should be permanently discontinued and not restarted after recovery. If the patient is well enough to take medication, CBV should be continued and TDF added as soon as possible. If necessary, all drugs should be stopped and CBV/TDF started soon after toxicity symptoms resolve.

See also section 2.10 below for further guidelines on the management of ABC reactions.

2.9.5 Safety monitoring

All serious adverse events must be recorded on the Serious Adverse Event Form and reported to the Local Trials Centre and MRC CTU. Grade 3 adverse events should be reported on the next scheduled follow-up unless they lead to treatment modification.

Data on SAEs will be reported, if required, to ethics committees (treatment assignment blinded) and will be tabulated and presented to the Data Safety Monitoring Committee (DSMC) (treatment assignment unblinded).

2.10 Hypersensitivity reaction to abacavir and management of safety - as provided by GSK.

Fatal hypersensitivity reactions have been associated with therapy with ABC. Patients developing signs or symptoms of hypersensitivity (which include fever; skin rash; fatigue; gastrointestinal symptoms such as nausea, vomiting, diarrhoea, or abdominal pain; and respiratory symptoms such as pharyngitis, dyspnoea, or cough) should discontinue ABC as soon as a hypersensitivity reaction is suspected. To avoid a delay in diagnosis and minimize the risk of a life-threatening hypersensitivity reaction, ABC should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases, gastroenteritis, or reactions to other medications). There have been infrequent reports of hypersensitivity reaction following reintroduction of ABC, where the interruption was preceded by a single symptom (e.g., rash, fever or gastrointestinal symptoms). On very rare occasions, hypersensitivity reactions have been reported in subjects who have stopped and restarted therapy, and who had no preceding symptoms of a hypersensitivity reaction.

ABC must not be restarted following a hypersensitivity reaction because more severe symptoms will recur within hours and may include life-threatening hypotension and death.

2.10.1 Description of hypersensitivity to Abacavir

In clinical studies, approximately 5% of patients receiving ABC develop a hypersensitivity reaction that in rare cases has proved fatal. This is characterized by the appearance of symptoms indicating multi-organ/body system involvement. The reaction can occur at any time during treatment with ABC, but the symptoms usually appear within the first six weeks of initiation of treatment (median time to onset is 11 days) and most often include fever, rash, gastrointestinal symptoms (nausea, vomiting, diarrhea, or abdominal pain), and lethargy or malaise. Other signs and symptoms may include respiratory symptoms (dyspnoea, sore throat, cough), musculoskeletal symptoms (myalgia, rarely myolysis, arthralgia), headache, paraesthesiae and oedema. Some patients with hypersensitivity reactions were initially thought to have acute onset respiratory diseases, gastroenteritis, or reactions to other medications. This delay in diagnosis of hypersensitivity has resulted in ABC being continued or re-introduced, leading to more severe hypersensitivity reactions or death. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of these diseases. Renal failure, hepatic failure and anaphylaxis have also been reported in association with hypersensitivity reactions.

Physical findings include lymphadenopathy and, occasionally, mucous membrane lesions (conjunctivitis and/or mouth ulceration) and hypotension. The rash is variable and may be absent, but often appears maculopapular or urticarial. Laboratory abnormalities that may accompany ABC hypersensitivity include elevated liver function tests, creatinine phosphokinase, creatinine or lymphopenia.

Symptoms related to this hypersensitivity reaction worsen with continued therapy and usually resolve upon discontinuation of ABC. Restarting ABC following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence of the hypersensitivity reaction may be more severe than on initial presentation and may include life-threatening hypotension and death. Subjects who develop a hypersensitivity reaction must discontinue ABC and must NEVER be re-challenged with ABC (ziagen or trizivir).

2.10.2 Information for patients

Subjects must be informed of the risk of a hypersensitivity reaction to ABC and provided with information to help them recognize the symptoms and signs associated with possible hypersensitivity reactions. Patients must be advised to contact the clinic immediately if they experience such symptoms.

Warning Card - All subjects receiving ABC should receive a wallet-size warning card provided by GlaxoSmithKline (GSK). As each subject is enrolled, the study site must assure that:

- a) The subject receives the warning card.(Information will be translated into local languages where necessary)
- b) The designated health care provider (e.g., physician, study nurse-coordinator, or pharmacist) reviews the signs and symptoms of hypersensitivity with the subject.
- c) The subject verbalizes an understanding of the steps to take in the event of a suspected hypersensitivity, including contacting the study site.

2.10.3 Medical management for possible hypersensitivity to abacavir

If a subject reports symptoms consistent with the diagnosis of ABC hypersensitivity, s/he should be instructed not to take any additional doses of ABC and should be evaluated at the clinic within 12 to 24 hours. All possible, suspected, implied, and/or probable cases of “ABC hypersensitivity” are to be reported as a SAE on the SAE pages of the CRF. ABC hypersensitivity CRF pages (Abacavir Hypersensitivity Reaction Record for Non-GlaxoSmithKline Clinical Trials Only) should also be completed and reported to GSK.

If the clinical presentation cannot be differentiated between hypersensitivity and another medical event (e.g. respiratory infection, gastroenteritis, or reaction to another medication), ABC must be discontinued.

Once the diagnosis of a hypersensitivity reaction has been made, the investigator should take the following steps:

- ◆ The patient should permanently discontinue ABC study medication
- ◆ Counsel the patient that ABC should never be re-started, as a life-threatening reaction may occur within hours. The patient should never be prescribed any ABC-containing product (e.g. ziagen or trizivir)
- ◆ Complete the Hypersensitivity CRF provided by GSK
- ◆ Complete the SAE form
- ◆ Obtain all hypersensitivity laboratory evaluations including chest x-ray if respiratory symptoms are present.
- ◆ The patient should return all unused ABC for disposal to prevent an accidental re-challenge.
- ◆ Symptomatic support for the acute reaction may include antihistamines and corticosteroids.
- ◆ Symptoms usually start to resolve within 24 hours after stopping therapy. Symptomatic support, such as intravenous fluids for those who develop hypotension, is advised. There are no clinical data demonstrating the benefit of antihistamines or

corticosteroids in the management of hypersensitivity. Nevertheless, symptomatic and/or supportive treatment may be reasonable.

2.10.4 Medical management for Abacavir rash not accompanied by systemic symptoms

The following guidance is provided for clinical management of subjects who experience rash alone in the absence of accompanying diagnosis of ABC hypersensitivity, systemic or allergic symptoms or signs of mucosal or target lesions. The toxicity ratings must be used to appropriately grade cutaneous events when recording AEs.

- ◆ For grade 1 or 2 rash, antihistamines or topical corticosteroids may be prescribed. Use of a Medrol pack is not allowed.
- ◆ Study medications should be continued. The patient's symptoms should be evaluated and followed aggressively for one week or until symptoms resolve or change. If additional symptoms develop, the patient should be re-evaluated in clinic.
- ◆ If the etiology of the rash can be definitively diagnosed as due to concurrent illness or other medical event, routine management should be performed and the documentation of the diagnosis provided.
- ◆ Subjects who develop a grade 3 or 4 rash (e.g., exfoliation, mucosal involvement, or target lesions [erythema multiforme]) or any evidence of Stevens - Johnson syndrome should have all study drugs discontinued and assessed further.
- ◆ Patients should be followed, even though study medications have been discontinued.

2.10.5 Fever and hypersensitivity to Abacavir

The onset of fever may herald hypersensitivity. Subjects reporting fever should be evaluated as above for the possibility of a hypersensitivity reaction to ABC. In the event of a clinical presentation consistent with hypersensitivity, ABC should be discontinued permanently, and the steps taken as stated above.

2.10.6 Special considerations following an interruption of abacavir therapy

If therapy with ABC has been discontinued and restarting therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the subject did not have symptoms of a hypersensitivity reaction. Subjects who have stopped ABC due to possible adverse reactions or illness should be advised to contact their doctor before restarting.

If hypersensitivity reaction cannot be ruled out, ABC should not be restarted.

There have been infrequent reports of hypersensitivity reaction following reintroduction of ABC, where interruption was preceded by a **single symptom**. When subjects who have discontinued ABC present with an indeterminate diagnosis of hypersensitivity (single symptom: rash, fever, malaise/fatigue, gastrointestinal symptoms or a respiratory symptom), the investigator should:

- ◆ Assess the probability that hypersensitivity preceded the interruption. It may be difficult to fully assess a patient's signs and symptoms if there has been a delay of more than a day between the patient stopping therapy and presenting to the physician. If there is doubt about the diagnosis, ABC should not be restarted.
- ◆ Assess the risk:benefit of reinitiating ABC

On very rare occasions hypersensitivity reactions have been reported in subjects who have stopped and restarted ABC therapy and who **had no apparent preceding symptoms** of a hypersensitivity reaction. If a decision is made to restart ABC in this setting, it should be assured that the subject can readily contact the site in the event that symptoms develop. Single missed doses require no special precautions. Subjects should be instructed to resume their normal treatment schedule. If an interruption of 3 or more days is noted, the subject should contact the study investigator. If it is determined that a hypersensitivity reaction is not present, the subject may resume treatment.

2.11 NORA SUBSTUDY FLOW SHEET

Table 8 NORA flow sheet

EVENTS	Screening Week -2	SUBJECT'S WEEK OF TREATMENT							
		Entry Week 0	2	4	8	12	16	20	24
Signed Consent		X							
History & Physical ¹	X	X	X	X	x	X	X	X	X
Symptom check list	X	X	X	X	X	X	X	X	X
Pregnancy Test ²	X								X
Haematology ³	X			X*		X*			X*
Biochemistry ⁴	X			X*		X*			X*
Lymphocyte Subsets ⁵	X					X*			X
Plasma storage ⁶	X	X		X		X			X
Adherence Determination ⁷				X	X	X	X	X	X

* Not returned to clinician in CMO arm.

¹ Clinical: including weight, WHO staging for HIV.

² See section 7.3.4 if positive.

³ Haematology: Hb, MCV, WBC, Lymphocytes, Neutrophils, Platelets.

⁴ Biochemistry: Blood Urea Nitrogen or Creatinine, AST or ALT, Bilirubin.

⁵ CD4, CD8, CD3 percentage and total lymphocyte count.

⁶ Take 6 ml blood into EDTA. Store DNA pellet (if feasible) See Appendix 7 for storage instructions.

⁷ See Appendix 8.0.

NB In addition to the above, patients will return 4-weekly to see the nurse, return used drug containers, and receive 4 weeks of ART

2.12 DART NORA Substudy Patient Information sheet

(to be given in addition to the DART information sheet for those eligible to participate in the NORA substudy. Patients participating in this substudy should not take part in the STI pilot)

Patient Information sheet for Nevirapine or Abacavir (NORA) Substudy

You have already been invited to take part in the DART study. If you consent you may be asked if you would like to be enrolled in the nevirapine (NVP) or abacavir (ABC) substudy (NORA). This information sheet gives you details about the substudy. Discuss it with others if you wish. Ask us if anything is not clear or if you would like more information. You will be given a copy of this information sheet to keep.

What is the purpose of NORA?

The purpose of this substudy is to compare the safety of abacavir (ABC) with nevirapine (NVP), both in combination with combivir (ZDV & 3TC) in 600 patients.

What will happen if I wish to take part in the substudy?

You will be required to give separate signed consent to take part. You will first be assigned to one of the two main DART study monitoring arms and then to either combivir with ABC and NVP placebo (inactive drug) or combivir with NVP and ABC placebo. Both allocations will be done by a computer programme to ensure an even balance of patients in each group. You and your doctor will not know which combination of drugs you are going to take (although if your doctor needs to find out s/he can do so). You will take the drugs and placebo every day for 6 months, following the instructions given and after 6 months you will continue taking drugs but without placebo.

How often will I need to attend the clinic?

You will have to come to the clinic 2 and 4 weeks after enrolment. After that you will be followed every 4 weeks. You will be asked if you have any problems and if you have taken all the drugs you were given (you must return any drugs you have not taken). You can ask questions and discuss any problems you have at these visits. Blood tests will be taken after the first 4 weeks and then at 12 and 24 weeks.

What are the disadvantages and risks of taking part?

All anti-HIV drugs can cause side-effects. If you experience what could be a side effect you should tell your doctor at your next clinic visit. Rarely, a reaction or hypersensitivity to ABC may develop. The earliest signs are mild fever, weakness and nausea. A rash may then develop, followed by vomiting, diarrhoea and muscle pain.

If you think you may have this hypersensitivity you must not take any more of your anti-HIV drugs and must come to the next weekday clinic. Your doctor will keep you under close observation. If it is

found that your symptoms are due to a particular drug, that drug will be replaced with another anti-HIV drug. If your doctor thinks you may have had hypersensitivity to abacavir, you will be told NEVER to take abacavir again.


What are the possible benefits of taking part?

The information we get from the substudy will help us to make the best use of these anti-HIV drugs for you and other people with HIV infection.

What happens at the end of the substudy?

The substudy will last for 6 months. After that, if you have improved with the treatment you will continue on your drugs and remain on the monitoring arm you were randomised to before the substudy. If you had any problems with treatment, your doctor would have changed your treatment and you will remain on your new drugs. You will continue to receive drugs and follow-up as in the main DART study.

2.13 DART NORA Substudy Patient consent form

Fill in with Forms 2-4 at Enrolment	DART TRIAL DART NORA CONSENT	
Centre: Entebbe <input type="radio"/> Harare <input type="radio"/> JCRC <input type="radio"/> Acad All <input type="radio"/>	Trial Consent Date: Day <input type="text"/> <input type="text"/> Month <input type="text"/> <input type="text"/> Year <input type="text"/> 2 <input type="text"/> 0 <input type="text"/> 0 <input type="text"/>	
Date/Year of Birth: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 1 <input type="text"/> 9 <input type="text"/> <input type="text"/>	Clinic/Hospital Number: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Age at Screening (if DOB not available): <input type="text"/> <input type="text"/> Initials: <input type="text"/> <input type="text"/> Male <input type="radio"/> Female <input type="radio"/>
DART Trial Number: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		

DART NORA SUBSTUDY CONSENT

A randomised double-blind phase II substudy trial to evaluate the toxicity of Abacavir compared with Nevirapine in combination with Combivir as first-line therapy in patients participating in the DART trial

NORA
(Nevirapine OR Abacavir)

- Please initial (or mark) box if you agree:
1. I have read/been read the information sheet for the NORA substudy and I understand what will be required of me if I participate in the substudy.
My questions concerning this substudy have been answered by: _____
 2. I understand that I will be given anti-HIV drugs for 4-5 years while I am in the DART study. After the study, my healthcare will be provided by the national health system.
 3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason and without affecting my normal care and management.
 4. I agree to allow blood samples to be taken and stored for testing later. I understand that I may not be given results of tests performed on stored samples.
 5. I am willing to allow access to my medical notes to check that the trial is being carried out correctly but understand that strict confidentiality will be maintained.
 6. I agree to take part in the NORA substudy.

Individual's signature (or thumbprint)	Print name	Date
Witness's signature	Print name	Date
Doctor's signature	Print name	Date

IMPORTANT: One signed original to be given to patient
 One signed original to be kept on file by the researcher
 One signed original to be kept in the clinic notes

CRF Version 1.4, December 2003

Appendix 3.0 Details of Antiretroviral Therapy

Detailed information on all drugs will be provided on regularly updated disk from EMEA website and in individual drug brochures

Drug (recommended dosing)	Class and major toxicities	Contraindications	Drug interactions
Zidovudine (Retrovir) 300mg twice daily (600mg daily)	NRTI Anaemia, leucopenia, neutropenia, nausea, vomiting	Cannot be used in patients with abnormally low neutrophil counts ($< 0.75 \times 10^9$ /litre) or abnormally low haemoglobin levels (< 7.5 g/dL) * Switch to another drug recommended if patient experiences grade 3 or 4 haematological toxicity. No co-administration with stavudine!	Co-administration with rifampicin decreases AUC of ZDV by 48%: in clinical practice doses are not adjusted. Products inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism (eg codeine, morphine, indomethacin, naproxen, oxazepam, cimetidine, dapsone) should be administered with caution.
Lamivudine (Epivir) 150mg twice daily or 300 mg once daily (300 mg daily)	NRTI Can be administered with or without food Nausea, vomiting, abdominal pain or cramps, headache, arthralgia	In moderate to severe renal impairment with creatinine clearance 30-50 ml/min change to 150mg once daily and if < 30 ml/min: dose reduction recommended to below 150mg daily using oral solution. Switch to another drug is often practised.	High doses of co-trimoxazole for treatment of PCP should be avoided Co-administration with intravenous ganciclovir or foscarnet is not recommended
Combivir 300mg zidovudine/ 150mg lamivudine twice daily	See Retrovir and Epivir	Dosage reduction recommended in reduced renal function (creatinine clearance < 50 ml/min) In severe hepatic impairment separate Epivir and Retrovir recommended to facilitate Retrovir dose adjustment. Switch to alternative drug is often practised.	See Retrovir and Epivir

* Note that, in DART, patients should not be recruited if neutrophils $< 0.5 \times 10^9$ /litre; patients with counts $0.5 - 0.75 \times 10^9$ /litre may be included (see section 6.2, page 23).

Drug (recommended dosing)	Class and major toxicities	Contraindications	Drug interactions
<p>DDI (Didanosine, Videx) 200 mg twice daily (or 400mg once daily) if <60kg: 125mg twice daily (or 250mg once daily)</p>	<p>Ingestion with food reduces the amount of didanosine absorbed by approximately 50%. Major toxicities: pancreatitis, peripheral neuropathy, abnormal liver function tests; cases of lactic acidosis (in the absence of hypoxemia), sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis</p>	<p>Extreme caution in patients with a history of pancreatitis</p>	<p>Medicines which can be affected by stomach acidity (eg. oral azoles such as ketoconazole and itraconazole), should be given at least 2 hours prior to dosing with Videx Co-administration of ddi with medicines that are known to cause peripheral neuropathy or pancreatitis may increase the risk of these toxicities. If treatment with other drugs known to cause pancreatic toxicity is required (e.g. i.v. pentamidine), didanosine should be suspended during such therapy wherever possible Plasma concentrations of some quinolone antibiotics (eg. ciprofloxacin) are decreased by administration with antacids contained in or administered with Videx. Tetracycline antibiotics (e.g. doxycycline) should not be taken with Videx.</p>
<p>D4T (Stavudine, Zerit) 40mg twice daily if <60kg, use 30mg twice daily</p>	<p>NRTI Should be taken on empty stomach Headache, chills, fever, abdominal pain, nausea, vomiting, myalgia, arthralgia, malaise, insomnia, depression Peripheral neuropathy, lactic acidosis, pancreatitis, hepatic impairment</p>	<p>In patients with ALT/AST >5 x ULN, D4T should be discontinued Patients with previous history of pancreatitis should be carefully monitored Treatment with D4T should be interrupted in peripheral neuropathy and re-introduced after resolution of symptoms (50% dose level may be considered) No co-administration with ZDV.</p>	

Drug (recommended dosing)	Class and major toxicities	Contraindications	Drug interactions
Tenofovir (Viread) 245 mg once daily 245 mg tablet is equivalent to 300mg of tenofovir disoproxil (as fumarate)	NRTI Consider interruption of TDF therapy if serum creatinine > 2.0 mg/dl (177umol/l) or serum phosphate < 1.0 mg/dl (0.32 umol/l) Most common side effects: diarrhoea, nausea, vomiting, flatulence (1 % discontinuance rate for GI side effects); grade 1 and 2 serum phosphate decreases requiring phosphate supplementation is some patients	Tenofovir should not be administered to patients with severe renal impairment. No data on patients with mild or moderate renal impairment: caution advised.	Nephrotoxic agents should be avoided but if they have to be administered concomitantly, weekly monitoring of renal toxicity should be considered. No interaction with lamivudine, indinavir or efavirenz In co-administration: AUC for dDI increased by 44%, with lopinavir/ritonavir: 30% increase in Cmax and AUC for tenofovir and about 15% decrease in the same parameters for lopinavir. However, in clinical practice dose adjustments are not made.
Nevirapine (Viramune) 200mg once daily for 14 days, followed by 200mg twice daily After treatment interruptions lasting >7days, restart with 200mg once daily	NNRTI Within first 6 weeks: Potential severe and life threatening skin reactions: Stevens Johnsons syndrome and toxic epidermal necrolysis or serious hepatitis/hepatic failure The majority of NVP associated rashes appear within first 6 weeks: dose escalation should NOT be instituted till rash resolves.	Severe hepatic failure NVP should not be re-administered to patients who discontinued this drug for severe rash, rash accompanied by constitutional symptoms, NVP induced hypersensitivity or clinical hepatitis. If AST or ALT > 5xULN, NVP should be stopped	Oral contraceptives should not be used as sole method of contraception as NVP co-administration may decrease the concentration of these agents. Ketoconazole should not be co-administered (replace with fluconazole) Compounds that are enzyme substrates for Cyp3A and CYP2B6 may have altered metabolism when co-administered with NVP and need to be carefully monitored: clarithromycin, cimetidine Rifampicin is Not recommended: rifabutin can be used instead Prednisone DOES NOT decrease NVP related rash.
Hard gel Saquinavir (Fortovase) (boosted) 1600mg plus 100mg ritonavir once daily	Protease Inhibitor Major toxicities: Hyperglycaemia and fat redistribution	Do not administer in severe renal or hepatic impairment	Should not be co-administered with rifabutin or rifampicin . Due to inhibition of CYP3A4, saquinavir should not be administered with compounds that are substrates for this enzyme; e.g. terfenadine, , midazolam, pimozone, ergot derivatives

Drug (recommended dosing)	Class and major toxicities	Contraindications	Drug interactions
Lopinavir/ Ritonavir (Kaletra) 133mg/33.3mg capsules, three capsules twice daily	Protease Inhibitor Major toxicities: Hyperglycaemia and fat redistribution Pancreatitis has been reported in patients with hyperglycaemia	Do not administer in severe hepatic impairment. Caution with severe renal impairment	No co-administration with rifampicin! Due to inhibition of CYP3A4, Kaletra should not be administered with compounds that are substrates for this enzyme; e.g. terfenadine, midazolam, pimozone, ergot derivatives Caution required when used with products known to induce QT interval prolongation e.g. clarithromycin, erythromycin Oral contraception effectiveness may be decreased.
Indinavir (Crixivan) 800mg three times daily	Protease Inhibitor Major toxicities: nephrolithiasis (adequate hydration of patients taking the drugs is recommended); Fat redistribution and hyperglycaemia	Do not administer in severe renal or hepatic impairment	No co-administration with rifampicin! Dose increase of rifabutin and dose reduction of indinavir are recommended when two compounds are co- administered. Due to inhibition of CYP3A4, Indinavir should not be administered with compounds that are substrates for this enzyme; e.g. terfenadine, midazolam, pimozone, ergot derivatives

Appendix 4.0 Toxicity Grading and Management

4.1 Table of Common Toxicity Criteria

Note: ULN denotes upper limit of local reference range (“upper limit of normal”)

	Grade 1	Grade 2	Grade 3	Grade 4
HAEMATOLOGICAL				
Haemoglobin	8.0-9.4 g/dl	7.0-7.9 g/dl	6.5-7.0 g/dl	<6.5 g/dl
Leucopenia	3.0-3.9 x10 ³ cells/μl	2.0-2.9 x10 ³ cells/μl	1.9-1.0 x10 ³ cells/μl	<1.0 x10 ³ cells/μl
Neutrophils	1.00-1.50 x10 ³ cells/μl	0.75-0.99 x10 ³ cells/μl	0.50-0.74 x10 ³ cells/μl	<0.50 x10 ³ cells/μl
Platelets	75-99 x10 ³ cells/μl	50-74 x10 ³ cells/μl	20-49 x10 ³ cells/μl	<20 x10 ³ cells/μl
Prothrombin time	>1.0-1.25 x ULN	>1.25-1.5 x ULN	>1.5-3.0 x ULN	>3.0 x ULN
Partial prothrombin time	>1.0-1.66 x ULN	>1.66-2.33 x ULN	>2.33-3.0 x ULN	>3.0 x ULN
Methaemoglobin	5-10.0 %	10.1-15.0 %	15.1-20.0 %	>20 %
BIOCHEMISTRY				
Hyponatraemia	130-135 mmol/l	123-129 mmol/l	116-122 mmol/l	<116 mmol/l
Hypernatraemia	146-150 mmol/l	151-157 mmol/l	158-165 mmol/l	>165 mmol/l
Hypokalaemia	3.0-3.4 mmol/l	2.5-2.9 mmol/l	2.0-2.4 mmol/l	<2.0 mmol/l
Hyperkalaemia	5.6-6.0 mmol/l	6.1-6.5 mmol/l	6.6-7.0 mmol/l	>7.0 mmol/l
Hypocalcaemia (corrected for albumin)	1.95-2.10 mmol/l 7.8-8.4 mg/dl	1.75-1.94 mmol/l 7.0-7.7 mg/dl	1.53-1.74 mmol/l 6.1-6.9 mg/dl	<1.53 mmol/l <6.1 mg/dl
Hypercalcaemia (corrected for albumin)	2.70-2.93 mmol/l 10.8-11.7 mg/dl	2.94-3.19 mmol/l 11.8-12.7 mg/dl	3.20-3.44 mmol/l 12.8-13.7 mg/dl	>3.44 mmol/l >13.7 mg/dl
Hypomagnesaemia	0.47-0.59 mmol/l 1.2-1.4 mg/dl	0.35-0.46 mmol/l 0.9-1.1 mg/dl	0.25-0.34 mmol/l 0.6-0.8 mg/dl	<0.25 mmol/l <0.6 mg/dl
Hypophosphataemia	0.58-0.72 mmol/l 2.0-2.4 mg/dl	0.44-0.57 mmol/l 1.5-1.9 mg/dl	0.30-0.43 mmol/l 1.0-1.4 mg/dl	<0.3 mmol/l <1.0 mg/dl
Hypoglycaemia	3.1-3.6 mmol/l 55-64 mg/dl	2.2-3.0 mmol/l 40-54 mg/dl	1.7-2.1 mmol/l 30-39 mg/dl	<1.7 mmol/l <30 mg/dl
Hyperglycaemia (fasting)	6.5-9.0 mmol/l 118-164 mg/dl	9.1-14.0 mmol/l 165-255 mg/dl	14.1-28.0 mmol/l 256-509 mg/dl	>28.0 mmol/l >509 mg/dl or ketoacidosis
Triglycerides (fasting)	1.8-2.2 mmol/l 150-190 mg/dl	2.3-5.6 mmol/l 191-470 mg/dl	5.7-10.0 mmol/l 471-830 mg/dl	>10.0 mmol/l >830 mg/dl
Triglycerides (non-fasting)	-	4.8-8.9 mmol/l 400-750 mg/dl	9.0-14.4 mmol/l 751-1200 mg/dl	>14.4 mmol/l >1200 mg/dl
Albumin	26-30 g/l 2.6-3.0 g/dl	20-25 g/l 2.0-2.5 g/dl	<20 g/l <2.0 g/dl	-
Bilirubin	>1.0-1.5 x ULN	>1.5-2.5 x ULN	>2.5- 5.0 x ULN	>5.0 x ULN
AST or ALT or GGT	1.25-2.5 x ULN	>2.5-5.0 x ULN	>5.0-10.0 x ULN	>10.0 x ULN
Alkaline phosphatase	1.25-2.5 x ULN	>2.5-5.0 x ULN	>5.0-10.0 x ULN	>10.0 x ULN
Amylase (total or pancreatic or salivary)	>1.0-1.5 x ULN	>1.5-2.5 x ULN	>2.5-5.0 x ULN	>5.0 x ULN
Creatinine	>1.0-1.5 x ULN	>1.5-3.0 x ULN	>3.0-6.0 x ULN	>6.0 x ULN
Creatinine kinase	>1.0-2.0 x ULN	>2.0-4.0 x ULN	>4.0-6.0 x ULN	>6.0 x ULN
Urea	1.25-2.5 x ULN	>2.5-5.0 x ULN	>5.0-10.0 x ULN	>10.0 x ULN
URINALYSIS				
Proteinuria	1+ or <0.3% or <3g/l or 200mg-1g loss/day	2-3+ or 0.3-1.0% or 3-10g/l or 1-2g loss/day	4+ or >1.0% or >10g/l or 2-3.5g loss/day	nephrotic syndrome or >3.5 g loss/day

	Grade 1	Grade 2	Grade 3	Grade 4
Haematuria	microscopic only	gross, no clots	gross and clots	obstruction <u>or</u> requiring transfusion
GASTROINTESTINAL				
Stomatitis/mouth ulcers	mild discomfort, no limits on activity	some limits on eating or talking	eating/ talking very limited	requiring IV fluids
Nausea	mild or transient discomfort, maintains reasonable intake	moderate discomfort <u>or</u> significantly decreased intake for <3 days	severe discomfort <u>or</u> minimal intake for ≥3 days	hospitalisation required
Vomiting	mild or transient; 2-3 episodes per day <u>or</u> mild vomiting lasting <1 week	moderate or persistent; 4-5 episodes per day <u>or</u> vomiting lasting ≥1 week	severe vomiting of all food/fluids in 24 hours <u>or</u> orthostatic hypotension <u>or</u> IV fluids required	hypotensive shock <u>or</u> hospitalisation required for IV fluids
Diarrhoea	mild or transient; 3-4 loose stools/day <u>or</u> mild diarrhoea lasting <1 week	moderate or persistent; 5-7 loose stools/day <u>or</u> diarrhoea lasting ≥1 week <u>or</u> nocturnal loose stools	bloody diarrhoea <u>or</u> orthostatic hypotension <u>or</u> >7 loose stools/day <u>or</u> requiring IV fluids	hypotensive shock <u>or</u> hospitalisation required for IV fluids
Clinical pancreatitis	mild abdominal pain, amylase <2.5x ULN, other causes excluded	moderate abdominal pain, amylase <2.5x ULN, other causes excluded	severe abdominal pain, amylase >2.5x ULN, hospitalisation required	severe abdominal pain, shock/ hypovolaemia, amylase>5x ULN, hospitalisation required
NEUROLOGICAL				
Headache	mild, no treatment	moderate <u>or</u> requires non-narcotic analgesia	severe <u>or</u> responds to first narcotic	intractable <u>or</u> requiring repeated narcotics
Consciousness	difficulty in concentration or memory	mild confusion or lethargy <50% waking hours	disoriented or stupor >50% waking hours	coma or seizures
Mood	mild anxiety or depression	treatment required for anxiety or depression	treatment and assistance required, severe depression, mania or anxiety	acute psychosis <u>or</u> hospitalisation
Psychosis	mild agitation <u>or</u> confusion	some limitation in activities of daily living and minimal treatment required	treatment and assistance required, severe agitation or confusion	toxic psychosis <u>or</u> hospitalisation
Cerebellar	slight incoordination <u>or</u> dysdiadochokinesia	intention tremor <u>or</u> dysmetria <u>or</u> slurred speech <u>or</u> nystagmus	ataxia requiring assistance to walk or arm incoordination interfering with activities of daily living	unable to stand
Motor	mild weakness in muscle of feet but able to walk <u>or</u> mild increase or decrease in reflexes	moderate weakness in feet (unable to walk on heels or toes), mild weakness in hands but still able to do most hand tasks, <u>or</u> loss of previously present reflex <u>or</u> development of hyperreflexia <u>or</u> unable to do deep knee bends due to weakness	marked distal weakness (unable to dorsiflex toes or foot drop) and moderate proximal weakness (eg in hands interfering with activities of daily living <u>or</u> requiring assistance to walk <u>or</u> unable to rise from chair unassisted)	confined to bed or wheelchair because of muscle weakness
Clinical myopathy	minimal findings	moderate myalgia <u>or</u> difficulty climbing stairs or rising from sitting position, able to walk, may need NSAID	moderate to severe myalgia needing NSAID, assistance required for walking or general activities	severe myalgia unrelated to exercise requiring narcotics, unable to walk <u>or</u> necrosis <u>or</u> oedema

	Grade 1	Grade 2	Grade 3	Grade 4
Sensory	mild impairment (decreased sensation eg vibratory, pinprick, hot/cold in great toes) in focal area or symmetric distribution	moderate impairment (moderately decreased sensation eg vibratory, pinprick, hot/cold to ankles) <u>or</u> joint position <u>or</u> mild impairment that is not symmetrical	severe impairment (decrease or loss of sensation to knees or wrists) <u>or</u> loss of sensation of moderate degree in multiple different body areas (eg upper and lower extremities)	sensory loss involves limbs and trunk
Parathaesia (burning, tingling etc)	mild discomfort, no treatment	moderate discomfort, requiring non-narcotic analgesia	severe discomfort <u>or</u> symptoms respond to narcotic analgesia	incapacitating <u>or</u> not responsive to narcotics
Peripheral neuropathy	mild paraesthesia, numbness, pain or weakness, not treated	moderate paraesthesia, numbness or pain, objective weakness, requires analgesic	severe, narcotic required, interferes with normal activity	intolerable, incapacitating, unable to walk despite narcotics, paralysis
RESPIRATORY				
Bronchospasm	transient, no treatment, 70-80% peak flow or FEV1	requires treatment, normalises with bronchodilator, 50-<70% peak flow or FEV1	no normalisation with bronchodilator, 25-<50% peak flow or FEV1, retractions	cyanosis, intubated <u>or</u> <25% peak flow or FEV1
CARDIOVASCULAR				
Cardiac arrhythmia	-	asymptomatic, transient dysrhythmia, no treatment	recurrent or persistent dysrhythmia, symptomatic treatment required	unstable dysrhythmia, hospitalisation and treatment required
Hypertension	transient, increase >20mm/Hg, no treatment	recurrent, chronic increase >20mm/Hg, requires treatment	acute treatment required, outpatient hospitalisation possible	hospitalisation required
Hypotension	transient, orthostatic hypotension no treatment	symptoms correctable with oral fluid treatment	IV fluid required, no hospitalisation required	hospitalisation required
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion, pain, ECG changes	tamponade <u>or</u> pericardiocentesis <u>or</u> surgery required
Haemorrhage	microscopic or occult	mild, no transfusion	gross blood loss <u>or</u> transfused 1-2 units	massive blood loss <u>or</u> transfused >2 units
OTHER				
Fever, oral, >12 hours	37.7-38.5°C	38.6-39.5°C	39.6-40.5°C	>40.5°C
Fatigue	normal activity reduced by <25%	25-50% decrease in normal activity	>50% decrease in activity, cannot work	unable to care for self
Hypersensitivity	pruritus without rash	localised urticaria	generalised urticaria <u>or</u> angioedema	anaphylaxis
Rash	erythema or pruritus	diffuse maculopapular rash <u>or</u> dry desquamation	vesiculation <u>or</u> moist desquamation <u>or</u> ulceration	exfoliative dermatitis <u>or</u> mucous membrane involvement <u>or</u> suspected Stevens-Johnson <u>or</u> erythema multiforme <u>or</u> necrosis requiring surgery
General	mild, transient, easily tolerated, no treatment	moderate, discomfort, interrupts usual activity, may require minor treatment	severe, considerable interference with usual activity, requires treatment or medical intervention	incapacitating or life-threatening, requires treatment and/or hospitalisation

4.2 Table of Clinical Signs, Symptoms, Monitoring and Management of Symptoms of Serious Adverse Effects of Antiretroviral Drugs that Require Drug Discontinuation (adapted from WHO guidelines^{ref 10} Annex 11B)

Adverse Effect	Possible Offending Drug(s)	Clinical Signs / Symptoms	Management
Acute hepatitis	Nevirapine (NVP); more uncommon with zidovudine (ZDV), didanosine (ddI), stavudine (d4T) (<1%); and protease inhibitors (PI), most frequently with ritonavir (RTV)	Jaundice, liver enlargement, gastrointestinal symptoms, fatigue, anorexia; NVP-associated hepatitis may have hypersensitivity component (drug rash, systemic symptoms, eosinophilia)	Monitor serum transaminases, bilirubin. All ARV should be stopped until symptoms resolve. NVP may need to be permanently discontinued.
Acute pancreatitis	ddI, d4T	Nausea, vomiting, and abdominal pain	If possible, monitor serum pancreatic amylase, lipase. All ART should be stopped until symptoms resolve. Restart ART with change to different NRTI, preferably one without pancreatic toxicity (e.g., ZDV)
Lactic acidosis	All nucleoside analogue reverse transcriptase inhibitors (NRTIs)	Initial symptoms are variable: a clinical prodromal syndrome may include generalized fatigue and weakness, gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain, hepatomegaly, anorexia, and/or sudden unexplained weight loss), respiratory symptoms (tachypnea and dyspnea) or neurologic symptoms (including motor weakness).	Discontinue all ARV; symptoms may continue or worsen after discontinuation of ART. Supportive therapy. Regimens that can be considered for restarting ART include a PI combined with an NNRTI and tenofovir
Hyper-sensitivity reaction	Abacavir (ABC) Nevirapine (NVP)	ABC: Constellation of acute onset of symptoms including: fever, fatigue, myalgia, nausea/vomiting, diarrhea, abdominal pain, pharyngitis, cough, dyspnea (with or without rash). While these symptoms overlap those of common infectious illness, the combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC is more typical of a hypersensitivity reaction. NVP: Systemic symptoms of fever, myalgia, arthralgia, hepatitis, eosinophilia with or without rash.	Discontinue all ARVs until symptoms resolve. The reaction progressively worsens with drug administration and can be fatal. Administer supportive therapy. Do not rechallenge with ABC (or NVP), as anaphylactic reactions and death have been reported. Once symptoms resolve, restart ARVs with change to different NRTI if ABC-associated or to PI- or NRTI-based regimen if NVP-associated.
Severe rash / Stevens-Johnson syndrome	Non nucleoside reverse transcriptase inhibitors (NNRTIs): nevirapine (NVP)	Rash usually occurs during the first 2-4 weeks of treatment. The rash is usually erythematous, maculopapular, confluent, most prominent on the body and arms, may be pruritic and can occur with or without fever. Life-threatening Stevens-Johnson Syndrome or toxic epidermal necrolysis (SJS/TEN) has been reported in ~0.3% of infected individuals receiving NVP	Discontinue all ARVs until symptoms resolve. Permanently discontinue NVP for rash with systemic symptoms such as fever, severe rash with mucosal lesions or urticaria, or SJS/TEN; once resolves, switch ART regimen to different ARV class (e.g., 2 NRTIs and tenofovir or 2 NRTIs and PI).

Adverse Effect	Possible Offending Drug(s)	Clinical Signs / Symptoms	Management
Severe peripheral neuropathy	ddI, d4T, (3TC – unusual)	Pain, tingling, numbness of hands or feet; distal sensory loss, mild muscle weakness, and areflexia can occur.	Stop suspect NRTI and switch to different NRTI that does not have neurotoxicity (e.g., ZDV, ABC). Symptoms usually resolve in 2-3 weeks.
Severe anaemia	ZDV	Severe pallor, tachycardia at rest Shortness of breath on exertion (SOBOE)	Stop ZDV and switch to another drug

4.3 Guide to management of toxicities

4.3.1 Grade 1 (clinical or laboratory(LCM arm only)):

- ◆ Continue study drugs

4.3.2 Grade 2 (clinical or laboratory(LCM arm only)):

- ◆ Continue study drugs
- ◆ If relevant, monitor more closely, and for LCM arm only, consider more frequent laboratory assessments.
- ◆ Work-up to exclude other causes

4.3.3 Grade 3 (clinical or laboratory(LCM arm only)):

- ◆ Repeat clinical observation within 72 hours for confirmation.
- ◆ LCM arm: if relevant, obtain repeat confirmatory laboratory results within 72 hours
- ◆ CMO arm: if clinically indicated, laboratory results can be requested
- ◆ Work-up to exclude other causes
- ◆ Clinician has the option of immediately stopping the study drugs if a confirmatory laboratory test cannot be performed within 72 hours, or if the clinician determines that the continuation of study drugs is unsafe while awaiting test results

4.3.4 Grade 4*(clinical or laboratory):

- ◆ If relevant, obtain confirmatory laboratory results within 72 hours and fill in adverse event form
- ◆ Work-up to exclude other causes
- ◆ Clinician has the option of immediately stopping the study drugs if a confirmatory laboratory test cannot be performed within 72 hours, or if the clinician determines that the continuation of study drugs is unsafe while awaiting test results
- ◆ For all confirmed Grade 4 toxicities that can be clearly attributable to one or more antiretroviral drug(s), consider stopping relevant drug(s) and switching to alternative drug(s) as indicated in section 8.1.4, page 33. If therapy needs to be stopped, stop all

drugs until toxicity resolves to \leq Grade 2. Then, restart therapy but discontinue the implicated drug(s) permanently and replace as indicated in section 8.1.4, page 33. If any doubt about management, discuss with the principal trial investigator

Appendix 5.0 Clinical progression and WHO Definitions

WHO clinical staging for HIV/AIDS

Clinical Stage 1:

Asymptomatic
Persistent generalised lymphadenopathy (PGL)
Performance scale 1: asymptomatic, normal activity

Clinical Stage 2:

Weight loss, <10% of body weight
Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis)
Herpes Zoster, within the last 5 years
Recurrent upper respiratory tract infections (e.g. bacterial sinusitis)
And/or performance scale 2: symptomatic, normal activity.

Clinical stage 3:

Weight loss, >10% of body weight
Unexplained chronic diarrhoea, >1 month
Unexplained prolonged fever (intermittent or constant), > 1 month
Oral candidiasis (thrush)
Oral hairy leukoplakia
Pulmonary tuberculosis, within the past year.
Severe bacterial infections (e.g. pneumonia, pyomyositis)
And/or Performance scale 3: bed-ridden, <50% of the day during the last month

Clinical stage 4:

HIV wasting syndrome, as defined by CDC¹
Pneumocystis carinii pneumonia
Toxoplasmosis of the brain
Cryptosporidiosis with diarrhoea, >1 month
Cryptococcosis, extra pulmonary
Cytomegalovirus (CMV) disease of an organ other than liver, spleen or lymph nodes
Herpes Simplex Virus (HSV) infection, mucocutaneous >1 month, or visceral any duration
Progressive multifocal leukoencephalopathy (PML)
Any disseminated endemic mycosis (e.g. histoplasmosis, coccidioidomycosis)
Candidiasis of the oesophagus, trachea, bronchi or lungs
Atypical mycobacteriosis, disseminated
Non-typhoid Salmonella septicaemia
Extra Pulmonary tuberculosis
Lymphoma
Kaposi's sarcoma (KS)
HIV encephalopathy, as defined by CDC²
And/or Performance scale 4: bed-ridden, >50% of the day during the last month

(note: Both definitive and presumptive diagnoses are acceptable)

¹ HIV wasting syndrome: weight loss of >10% of body weight, plus either unexplained chronic diarrhoea (>1 month), or chronic weakness and unexplained prolonged fever (>1 month).

² HIV encephalopathy: clinical finding of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection that could explain the findings.

Appendix 6.0 Patient Information sheet and Consent Forms (Templates)

6.1 Patient information sheet for DART study

DART

Development of AntiRetroviral Therapy in Africa for adults infected with HIV.

Patient information sheet

You are being invited to take part in a research study. Please read this information carefully or have someone read it to you. You will be given a copy of this form to keep. Discuss it with others if you wish. Ask us if you would like more information. Take time to decide whether or not you wish to take part. If you are already registered with a current health system provider (e.g. TASO in Uganda), joining this work will not affect your rights to any other benefits it offers.

If you decide not to take part now or to withdraw from the study later, this will not influence the care you receive now (e.g. if you are a TASO member you will still get all your benefits from TASO).

What is the reason for doing the study?

HIV infection cannot be cured, but taking anti-HIV (antiretroviral) drugs can control it. We want to find out how best to use anti-HIV drugs so that the treatment is safe and effective. At present doctors use regular blood tests to see how the drugs are working and to check for side-effects. We want to find out whether the drugs can be taken without doing many blood tests. We also want to find out if the drugs need to be taken all the time or can they safely be taken with breaks (3 months on drugs, 3 months off).

How can I join the study?

After reading this information sheet you will be asked to give consent to be screened, which will involve being seen by the doctor and giving a blood sample. After two weeks you will be told whether you are eligible for the study and asked to sign a DART study consent form if you choose to participate.

What will happen if I take part?

You will be started on 3 anti-HIV drugs and you will be assigned to one of two groups:

- **clinical monitoring-only group**
- or
- **clinical and laboratory monitoring group**

In the **clinical monitoring-only group** your doctor will make decisions about your treatment based only on your symptoms. The results of your blood tests will be monitored independently and your doctor will be informed if there is a problem.

In the **clinical and laboratory-monitoring group** your doctor will make decisions about your treatment based on your symptoms and the results of your blood tests.

You will be asked to attend clinics 2 and 4 weeks after entry to the study, then every 4 weeks to see the nurse and every 3 months to see the doctor and to provide blood. At each visit you will be given a supply of anti-HIV drugs and asked to follow exact instructions on how to take these drugs.

It is very important that you do not miss any doses and do not share your medication with others.

If anti-HIV drugs are not taken properly, they will lose their effect, as the virus becomes resistant. Other medicines should only be taken on the advice of your doctor. You will be counselled to practice safe sex, as anti-HIV drugs cannot prevent transmission of HIV infection to sexual partners. If you do not attend your clinic visit, we would like to send a field-worker to your home to find out how you are.

After you have been taking anti-HIV drugs for 6 months, if your immune system has improved (CD4 count greater than 200cells/mm³) you will be assigned into one of two groups (by computer):

- interrupted treatment (3 months on and 3 months off treatment)

or

- continuous treatment

If your immune system has not improved enough at 6 months, you will be examined again at 12 months. If your CD4 count then is greater than 200 cells/mm³, you will be eligible to be assigned to either interrupted or continuous treatment.

Treatment interruption pilot study

The first 100 patients who interrupt treatment will have blood tests and visits every month. Independent experts will look at the results on these 100 patients and if they find that treatment interruption is safe, all other patients with good response to treatment at 6 or 12 months will be assigned to either interrupted or continuous treatment. The pilot study will last for 6 months. After that, if you have no problems with interrupted treatment you will continue to interrupt drugs. If you had any problems with interrupted treatment, your doctor may suggest you take drugs continuously. After the pilot, you will continue on the monitoring arm you were assigned before the pilot. You will continue to receive drugs and follow-up as in the main DART study.

Blood samples

Blood tests may be done whenever you see the doctor. This may cause some discomfort and/or bruising in some patients. About two tablespoons of blood will be taken at one time. Some blood may be stored for later testing and you may not be given these results.

What drugs will be used in the DART study?

1. combivir (zidovudine + lamivudine in one pill)
2. tenofovir
3. nevirapine
4. didanosine
5. stavudine
6. saquinavir with ritonavir or other similar drugs from the same group

When you start the trial you will be given combivir with a third drug. The third drug will be tenofovir in Uganda and tenofovir or nevirapine in Zimbabwe. We will supply drugs for the duration of the study (4-5 years). After the study, your care will be provided by the national health system (or TASO in Uganda) including provision of anti-HIV drugs in line with current government plans.

Side effects

Anti-HIV drugs, like all drugs, have side effects, which are sometimes serious (less than 5%). If you experience symptoms tell your clinic doctor at your next visit, or if you are worried you should come to the clinic as soon as possible. It may be necessary to stop the drug(s) after which the problem usually goes away. We can replace drugs causing problems with other drugs.

Effects of drug interruption

During drug interruption it is possible that your HIV disease may get worse. If you get symptoms between visits you should come to the clinic. Your doctor may restart your treatment early (before the end of 3 months) and if problems continue when you are back on treatment, your drugs may be changed.

Pregnancy

HIV treatment given early in pregnancy may harm the unborn child. Pregnant and breastfeeding women will not be entered into this trial. A pregnancy test will be carried out at screening and at regular intervals during the study and women will be encouraged to avoid becoming pregnant during the trial. If a woman does become pregnant while in the trial, treatment will be continued without interruptions.

Confidentiality

Information about you will be kept confidential and will not be made available to anyone who is not connected with the study without your consent.

If you would like more information about this work please ask the doctors, nurses or counsellors. If you still need more information, call:

Insert names and telephone numbers as appropriate for each trial site

Name:

Telephone Number:

6.2 Consent for Screening for the DART Trial

fill in with Forms 0 & 1	DART TRIAL DART SCREENING CONSENT
-----------------------------	--



Centre: Entebbe Harare JCRC

Screening Consent Date: Day Month Year

Clinic/ Hospital Number:

Date/Year of Birth:

Age (if DOB not available):

Initials:

Male Female

DART TRIAL SCREENING CONSENT

I have read the information sheet for the DART trial and would like to be screened to see whether I am eligible for this trial.

I understand this will involve being seen by the doctor, who will ask questions about my health and my household, and having some blood taken.

Individual's signature (or thumbprint)	Print name	Date

Witness's signature	Print name	Date

Doctor's signature	Print name	Date

6.3 Patient consent form for DART Trial

fill with Forms 2-4 at Enrolment	DART TRIAL DART TRIAL CONSENT
--	--



Centre: Entebbe Harare JCRC

Trial Consent Date: Day Month Year 2 0 0 Clinic/ Hospital Number

Date/Year of Birth: 1 9 Age at Screening (if DOB not available) Initials Male Female

DART TRIAL CONSENT

A randomised trial of monitoring practice and structured treatment interruptions in the management of antiretroviral therapy in adults with HIV infection in Africa

DART
(Development of Anti-Retroviral Therapy in Africa)

- Please initial box if you agree:*
- I have read/been read the information sheet for the DART study and I understand what will be required of me if I participate in the study.
My questions concerning this study have been answered by:

 - I understand that I will be given anti-HIV drugs for 4-5 years while I am in the DART study. After the study, my healthcare will be provided by the national health system.
 - I understand that I may withdraw from the study at any time, without giving a reason and without affecting my normal care and management.
 - I agree to allow blood samples to be taken and stored for testing later. I may not be given results of tests performed on stored samples.
 - I am willing to allow access to my medical notes to check that the trial is being carried out correctly but understand that strict confidentiality will be maintained.
 - I agree to take part in the DART study.**
 - I also agree to take part in the treatment interruption pilot study if asked to do so.

Individual's signature (or thumbprint)	Print name	Date

Witness's signature	Print name	Date

Doctor's signature	Print name	Date

IMPORTANT: **One signed original to be given to patient**
One signed original to be kept on file by the researcher
One signed original to be kept in the clinic notes

Appendix 7.0 Handling and Storage of Specimens

7.1 Bloods

7.1.1 Processing of EDTA blood for Plasma and cell store

For best results, centrifuge within 2 hours of drawing blood. If the time to processing is not within the same working day, **do not proceed**.

1. Centrifuge at 1500g for 15 minutes to separate cells from plasma.
2. Using a sterile pipette, collect the plasma more than 5mm above the buffy cell coat layer (grey layer above red cell layer).
3. Place the plasma, using up to three aliquots, in the cryovials provided for the trial. A minimum of two aliquots is required. Routinely three cryovials of plasma and one cryovial containing the DNA pellet (if feasible) should be stored at each visit.
4. Label the cryovials with the patient "PLASMA" identification labels
5. Store cell pellet for later DNA isolation (if feasible). After plasma has been removed transfer the cell pellet into cryovial
6. Label the cryovials with the patient "CELLS" identification label and store at -80°C (if not possible then -20°C)

7.1.2 Storage of samples

1. Store within 4- 6 hours of drawing blood at -70°C (temperatures to -50°C allowed if this is not available). Place upright in the cryobox provided for the trial.
2. Add the Patient ID label to the Specimen Storage Log for sample. Complete the details for type of specimen processed, visit month, total number of tubes and storage temperature. Start a new log sheet when either the sheet is full or when starting to fill a new cryobox.

Appendix 8.0 Adherence protocol



FORM 14	DART TRIAL ADHERENCE
---------	---------------------------------

Centre: Entebbe Harare JCRC

Date Form Completed: Day Month Year 2 0 0

Clinic/ Hospital Number:

Date/Year of Birth: 1 9

Age at Screening (if DOB not available):

Initials: Male Female

DART Trial Number:

CMO LCM

Please tell us if you have been able to take your anti-HIV treatment as planned.
You do not have to answer all the questions if you do not want to.
A NURSE SHOULD HELP YOU COMPLETE THIS FORM

1. Are you late for this scheduled visit? (tick box) Yes No If yes, specify number of days late
2. During the past 4 days, on how many days have you missed taking all (or part) of your HIV drug doses?
1 day 2 days 3 days 4 days No days
3. Indicate in the box below when you took your drugs. Write the names of anti-HIV drugs in the first column. Put an 'X' if you took your drugs and put '0' if you missed a dose on each day.

Name of HIV drug	Did you take your drug?							
	Yesterday		2 days ago		3 days ago		4 days ago	
	am	pm	am	pm	am	pm	am	pm

4. Some people find that they forget to take their pills on the weekends. Did you miss any of your anti-HIV drugs last weekend (Saturday or Sunday)? (tick box)..... Yes No
5. Do any of your anti-HIV drugs have special instructions, such as "take with food", or "on an empty stomach"? (tick box) Yes No
If yes, how often did you follow these special instructions over the last 4 days? (tick box)
Never Some of the time About half of the time Most of the time All of the time
6. Which one (if any) of your anti-HIV drugs is the easiest to take? (write in here): _____
7. Which one (if any) of your anti-HIV drugs is the most difficult to take? (write in here): _____
8. When was the last time you missed any of your anti-HIV drugs? (tick box):
Within the last week 1- 2 weeks ago 2- 4 weeks ago 1- 3 months ago
More than 3 months ago Never
9. **(Complete at scheduled doctor visit only)** People may miss taking their anti-HIV drugs for many reasons. Here is a list of possible reasons. If you never miss your drugs do not answer this question

In the past month how often have you missed taking your anti-HIV drugs because you:	Never	Rarely	Sometimes	Often
a) Were away from home?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b) Were too busy with other things?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c) Simply forgot?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d) Had too many pills to take?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e) Wanted to avoid side-effects?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f) Did not want other people to notice you taking pills?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g) Had a change in daily routine?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h) Felt like the drug was toxic or harmful?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i) Were asleep through the dose time?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
j) Felt sick or ill?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
k) Felt depressed or overwhelmed?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
l) Had a problem taking pills at a specified time (with meals or on an empty stomach)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
m) Ran out of pills?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
n) Felt good?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Appendix 9.0 Post DART Trial issues

The DART trial, as with all clinical trials, is funded for a specific time-limited period by the funding bodies involved. Drugs will be provided for the duration of the trial for up to 5 years for each patient.

It may be expected that as all patients in the trial will be receiving HAART, many patients will be alive at the end of the trial, and still be benefiting from ART. For them cessation of therapy would not be appropriate. The various study sites in Uganda and Zimbabwe have made this dilemma clear in their ethical submissions. The DART team has initiated collaboration with the governments in Uganda and Zimbabwe and external sponsors to address these concerns and ensure that DART trial is entirely ethically sound and acceptable to the countries. Both Zimbabwe and Uganda have applied to the Global Fund and it is likely that access to ARV will expand if these applications are successful. It is expected that post-trial healthcare for the patients will be obtained within the framework of this partnership.

This partnership with local health authorities also includes collaborations with:

- The Ugandan Ministry of Health Task Force set up to deliver more drug treatment for Ugandan citizens and to establish the mechanisms of drug provision by the Government.
- The Academic Alliance which has recently established in Kampala with the aim to set up a large treatment centre for ART.
- The large and medium sized businesses to seek to derive support from the companies for long-term ART after the trial of their employees.
- Medical insurance companies who are taking an active interest in the issues around ART and are considering ways to provide ART for their clients.

The DART team is also working to establish a “Lake Victoria” Fund in Uganda as a charitable body with an initial donation of £100,000 already pledged from the Rock House Foundation, UK (Mr Martin Rossiter). We expect that businesses will also contribute to this fund; and we will have regular fund-raising activities run by the LakeVictoria Fund. This will be the safety net for those who fall through the private public partnership mechanisms and need financial support for long-term drug therapy and social support.