



**TRI-NATIONAL TRIAL 1:
Options In Management with Antiretrovirals**

A Randomised Controlled Trial To Determine The Optimal Management of Patients with HIV Infection for Whom First and Second-Line Highly Active Antiretroviral Therapy Has Failed

PILOT STUDY: Options in OPTIMA

To be used in conjunction with the full OPTIMA protocol version 1.1 19 march 2002 UK

**Conducted in the
United Kingdom**

(Protocol ISRCTN 19619965)

U.K Pilot Study

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1. Background

The OPTIMA trial is an international multicenter randomised trial in patients with HIV infection whose antiretroviral therapy (ART) has failed and who have been exposed to all three classes of antiretroviral drugs. The trial is addressing two questions in a factorial design: (i) is a combination of at least five drugs (Mega ART) better than four or less drugs (Standard ART)? and (ii) does an antiretroviral drug free period (ARDFP) before starting a new regimen improve the chance of success? The trial is being conducted in the US by the Department of Veterans Affairs (VA), in Canada by the CTN funded by the CIHR and in the U.K by the MRC through its CTU. The trial recruitment started in June 1, 2001 and has been much slower than anticipated in all three countries.

The reasons for the poor accrual in the U.K are not related to one specific issue but rather to a combination of many factors.

First there is a much smaller than anticipated pool of eligible patients than was initially anticipated. Drugs such as Kaletra, Tenofovir and T20 have helped many 'salvage' patients. Trials of new drugs are also having difficulties in recruiting from the low CD4/highly drug experienced population but it is proving most difficult to co-enrol in these trials and OPTIMA. Sites are aware that they can enrol into OPTIMA first and then add the new drug when the new regimen is started. Agreement has been reached with Roche for patients being considered for open access T20 trial where OPTIMA would be encouraged as a strategy before starting on T20. However, some patients are unwilling to consider a drug free period before they start a new combination. Indeed a number of patients have already discontinued ART to await a new drug combination and therefore would not be eligible for OPTIMA.

Other problems include a reluctance to be randomised to both parts of the trial. Patients' preferences seem equally split between the strategies and many who would be willing to be randomised to Mega-ART or Standard ART would not consider a ARDFP and vice versa. Some doctors do not feel it is appropriate to consider both strategies in OPTIMA while they have new drugs to offer to patients. It is also felt that the patients that are potentially eligible for OPTIMA are not likely to exhibit the degree of commitment necessary to adhere to the protocol. Many of the patients who fulfil the criteria for OPTIMA come from this group.

Mega-ART is not generally prescribed in the U.K due to cost, and whilst a subvention from the NHS was gained to supplement the payments made by MRC, these payments were insufficient to cover the costs of most Mega-ART regimens. (The payment took into account the savings made when on the ARDFP.)

A wide range of interventions has been instigated to stimulate recruitment in the U.K. These include increased resources to help sites identify eligible patients, a detailed patient leaflet with a wide circulation list (4,500 were distributed, 2,700 of these were directly mailed to readers of HIV Treatment Bulletin, who are health care professionals and people living with HIV), and a new website. All doctors treating people with HIV were written to informing them of this study and suggesting a shared care option to some small centres with the aim of increasing the number of participating centres in order to ensure the widest possible access to this trial for eligible patients.

Regular contact is maintained with the sites in a number of ways. Direct telephone contact from the project manager and trial physician, mail outs, newsletters, teleconferences, investigator meetings both at international conferences and national meetings and site visits.

The U.K also has contacted 3 countries not participating in the collaboration with the view of extending the study to these countries. This was unsuccessful.

At the most recent meeting of the TSC it was agreed to amend the total sample size for the trial from 1700 to 500 as new information from the trial itself and from other similar trials had indicated a that the original

conservatively estimated event rates were too low. Even with the new smaller sample size, at the current rate, recruitment will not be completed until 2005 and there are concerns whether the U.K can realistically achieve and maintain an accrual rate of one patient per month. At this level of recruitment it is difficult to maintain the profile of the trial and lack of familiarity with the trial procedures becomes a deterrent to many clinical centres. There is no doubt that such a slow rate of recruitment is difficult to maintain, even if the clinicians consider that the questions are still important.

2. Proposed amendment to the trial in the U.K

At the recent meeting of the Trial Steering Committee for the OPTIMA Trial a proposal to amend the trial in the U.K was discussed with the aim of increasing recruitment. Although it may be possible to recruit one patient a month it is very difficult to sustain the enthusiasm and interest in the trials in the clinical sites and at the co-coordinating centre in the U.K.

It is clear that a number of potentially eligible patients are not joining OPTIMA because they are unwilling to accept both randomisations. It is therefore proposed that for such patients the possibility of randomisation within one of the strategies rather than both is offered. Randomisation within the 2X2 factorial design will still be the first and preferred option.

This will mean that the number of patients who will be randomised to mega-ART or standard ART will be increased to include patients who:

1. are unwilling to accept an ARDFP,
2. have already stopped ART.

Similarly patients will be randomised to ARDFP or no ARDFP who:

1. want to take (or are already taking) mega-ART,
2. do not want to take mega-ART,
3. the Trust will not fund mega-ART.

Clinicians will still encourage patients to randomise within both comparisons (option 1, See Flow sheet). If however, patients select only one comparison (option 2 or 3, See Flow sheet) the clinician will, prior to randomisation, ask the patient:

1. whether they will be taking mega-ART or standard ART if entering the ARDFP or no ARDFP comparison;
2. whether they will or will not have an ARDFP if entering the mega-ART or standard ART comparison.

The randomisation will be stratified by the chosen option and this will be taken account of in the analysis via stratification, so that for the main effects, comparison between strategies will only be made within options and not between options. Patients entering only one randomisation can only be included in that main comparison, and will not contribute to the test of interaction (synergy), e.g. whether the effect of mega-ART relative to standard ART depends on whether the treatment was preceded by an ARDFP or not.

The disadvantage of this proposal is that to answer both the questions addressed in the trial the total number of patients will have to be increased. For each patient who would have been randomised within the factorial design (Option 1) it will require two (one in Option 2 and one in Option 3) to provide the same amount of information for the main comparisons. The aim will continue to be to recruit patients to Option 1 and only to offer Option 2 and 3 where the patients and/or the clinician is not willing to accept the double randomisation. However, preliminary discussions with several of the major centres in the U.K indicate that the number of patients may increase to 3 or four a month if this modification is introduced. If it does increase recruitment to this level in the U.K, extending to Canada might be considered as the rate

of recruitment could then potentially be increased to such a level that accrual could be completed more rapidly. However for the trial to be adequately powered to address both questions without substantially increasing the number of patients required, it is important that the majority of patients are randomised within Option 1, the original factorial design.

It was therefore decided to explore the feasibility of the proposed modification on a pilot basis in the U.K and to monitor the impact on recruitment over a 6-month period. After this time and a review of recruitment in all three countries a decision would be made to either adopt the protocol modification formally in one or more of the countries or to continue with the original design.

3. Implications of the modification

The modification has no implications for the trial or protocol, except:

1. The possibility of randomisation to Options 2 or 3 will be offered to those patients and/or clinicians who are not willing to accept randomisation to the factorial design.
2. Patients choosing Option 2 will be asked to choose whether or not to have an ARDFP (or may have already had one) before they are randomised and similarly those choosing Option 3 will have to decide between Standard or mega-ART. The randomisation form will be amended accordingly.
3. The randomisation schedule will be amended in the U.K to include stratification by Options 1, 2 or 3.
4. The analysis plan will be modified to take into account the change above.
5. The Patient information sheet will be amended to give details of the choice open to potential participants.

There will be no other change to the protocol. If the pilot phase does not demonstrate an increase in recruitment, these changes will not be adopted.

4. Impact on the participants

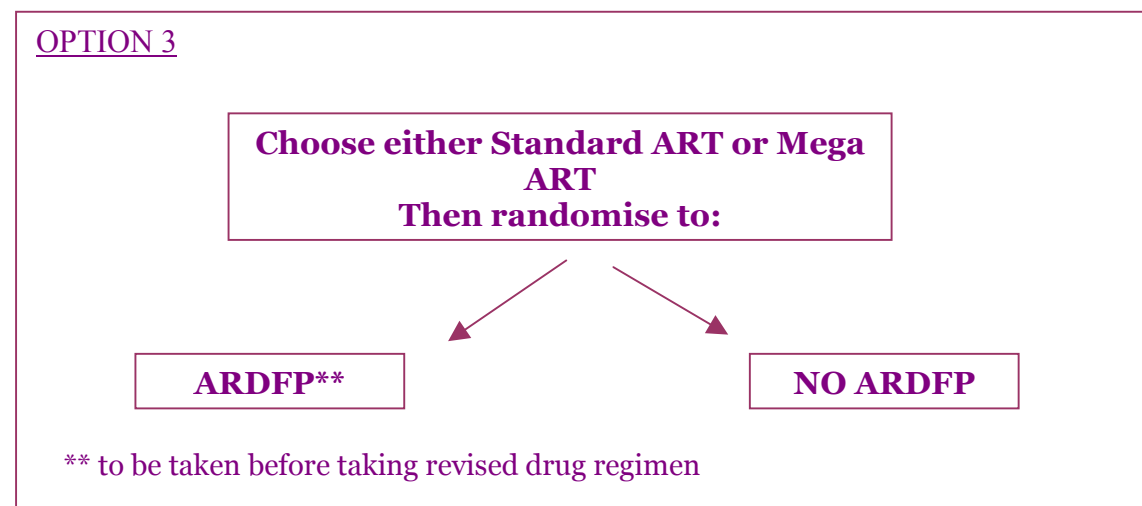
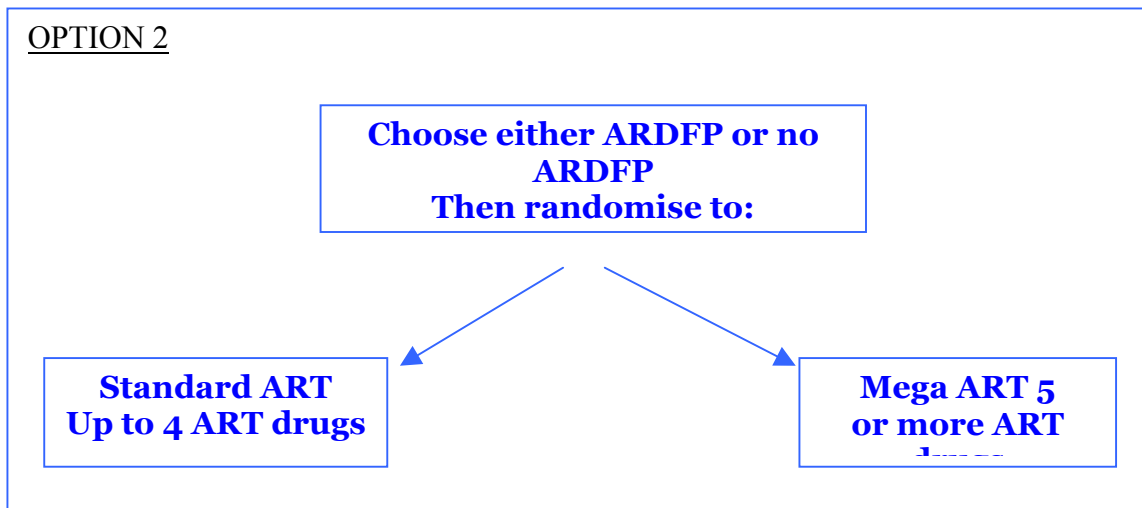
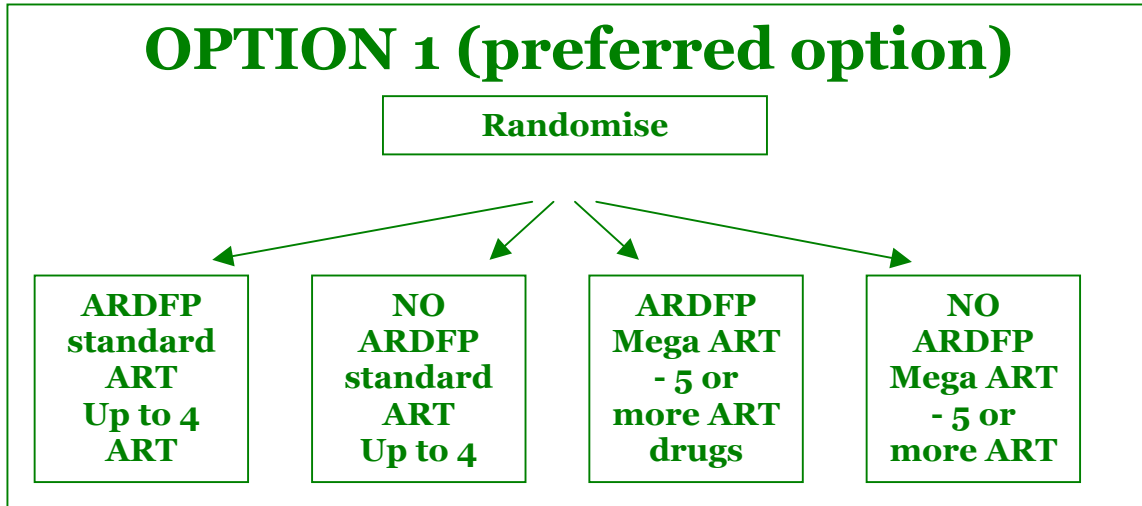
As the trial will not be modified in any way apart from allowing the choice between the three randomisation options which increase patient choice, there are no specific implications for participants. All study procedures including clinical assessments, laboratory investigators and biological specimen collection will be exactly as in the original protocol.

5. Review

The pilot study will be reviewed after it has been in place for 6 months to assess the impact on recruitment and a decision made as to whether to formally amend the protocol in the U.K and whether to make similar changes in one or both of the other two countries. The proposed criteria for success are an increase in recruitment in the U.K to an average of 4 patients per month (or 3 with at least one patient randomised within Option 1).

6. Flow Chart

Design of the OPTIMA Pilot Study
Patients / Doctors choose one of the 3 OPTIONS below



UK Patient Information and Consent Form

[Hospital headed paper]

Study title:

TNT 1: A randomised controlled trial to determine the optimal management of patients with HIV infection for whom first and second-line highly active antiretroviral therapy has failed:

“OPTIMA”

(Options in Management with Antiretrovirals)

Part A. Patient Information

Dated 3rd April 2003. Use with final protocol version 1.1 dated 19 March 2002 plus UK pilot study.

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?

The overall purpose of the main OPTIMA study is to find the best way of treating HIV infection after several of the most effective drug combinations have failed. The study will compare the risks and benefits of treatment using HIV drugs that are currently available, in the following two new ways:

- **Having a drug-free period**

We will test whether having a drug-free period, where you stop taking all HIV drugs for a period of three months, will improve your body's response to the drugs when you start taking them again. We will compare this approach to starting a new combination of drugs straight away.

- **Increasing the number of drugs**

We will test whether increasing the number of HIV drugs that you take to five or more will improve your body's response to the drugs. We will compare this approach, called 'mega-ART', to 'standard-ART' where you are treated with up to four HIV drugs. For both of these approaches, you and your doctor will choose which drugs you take. The decision will be guided by a resistance test that shows which drugs your HIV is sensitive to. It is the way drugs should be used that we are considering, not the effect of individual drugs being used.

You can join this study in one of three ways:

- **Option 1**

As in the main OPTIMA study, you will be randomised (similar to tossing a coin or rolling a dice) to both parts of the study. You will have a drug-free period of three months or no drug-free period and then receive either 'standard ART' or 'mega-ART' treatment.

- Option 2
You can choose whether or not to have a drug free period, and then be randomised for how many drugs you will take.
- Option 3
You can choose how many drugs you will take, and then be randomised to whether you will have a drug free period or not.

For example, if you decide that you do not want to take 'mega-ART' (more than 5 drugs) but don't mind whether or not your drugs are stopped for a short period, you could choose option 3. However, if you do not like the idea of stopping all of your drugs, you could go for option 2 and only enrol in the comparison of 'standard-ART' against 'mega-ART'. Similarly, if you do like the idea of not taking your drugs for a short period or you have already stopped your drugs for a period, you could also go for option 2.

We are offering options 2 and 3 to patients in the UK as a pilot study. The purpose of this pilot study is to see if offering these choices gives more patients the chance to take part in the study and helps us to find out the answers to the study questions sooner. If this study is successful, these options may become available to patients outside the UK and we will use information from this study to contribute to the final analysis of the study. If it is not successful, the information we collect about patients will still be valuable to the trial investigators, for example, in planning future research.

We will recruit people for the study over a period of four and a half years, and continue for one year after the last person has been recruited.

Why have I been chosen?

The study is being conducted in approximately 500 patients with HIV infection in the UK, Canada and the USA. You should be on combination HIV treatment now and have taken at least two different HIV drug combinations as part of your treatment including some from all three classes of HIV drugs. To join the study you need to have results from two recent blood tests showing a CD4 cell count less than 300 with a viral load above 2,500 copies.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. Even if you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw, or a decision not to take part, will not affect the standard of care you receive.

What will happen if I take part?

You will be involved in the study for between one to 4 and a half years, depending on when you join. If you sign the consent form you will be screened for the study by having a medical check-up and by having blood tests for safety, to check your CD4 cell count and viral load (if not done within 30 days) and for a resistance test. Some blood will also be frozen for storage. The resistance test will determine if your HIV is sensitive or resistant to available HIV drugs. In all, about 40ml (8 teaspoons) of blood will be collected. Women will also have a pregnancy test on a urine sample.

When the screening results are available, you can enter the trial. In the main OPTIMA trial you will be randomised (allocated by computer) to one of four treatment groups and have an equal chance of being allocated to either one (Option 1). However if you do not want one or more of the treatment groups in Option 1, you can choose either Options 2 or 3.

Option 1 the main OPTIMA trial; to be randomised to one of four groups.

- An HIV drug free period of 3 months followed by an HIV treatment with up to 4 drugs ("standard ART")

- An HIV drug free period of 3 months followed by an HIV treatment with 5 or more drugs (“mega-ART”)
- Immediate start of an HIV treatment with up to 4 drugs (“standard ART”)
- Immediate start of an HIV treatment with 5 or more drugs (“mega-ART”)

Option 2 you and your doctor to choose to have a drug free period or not then you will be randomised to either standard treatment up to 4 drugs or mega-ART 5 or more drugs.

Option 3 you and your doctor to choose either standard treatment or mega-ART then you will be randomised to either a drug free period before taking the new drug treatment or not.

The results of the resistance test will be used to help your doctor to select the HIV drugs. He or she will select HIV drugs that are not likely to upset you. If you are allocated to or choose an HIV drug free period of 3 months at trial entry, you will not be told whether your HIV treatment will be with up to 4 drugs (“standard ART”) or with 5 or more drugs (“mega-HAART”) until the time when you re-start HIV treatment. Your doctor can select any HIV drug currently available, including unlicensed drugs which are only available in expanded access programmes or named patient schemes and investigational drugs. This is an open trial and you will know which HIV drugs you are taking.

At trial entry, you will have a medical check-up and examination, be asked to complete a questionnaire about your current health and have blood tests in a fasting state - that is, after not having eaten for at least 8 hours. In all, about 60ml (12 teaspoons) of blood will be taken.

If you choose or are allocated to have an HIV drug free period at trial entry, you will need to visit the clinic 6 and 12 weeks after trial entry. You will be scheduled to re-start HIV treatment at week 12 but this can be brought forward if your CD4 cell count falls too quickly from trial entry. After re-starting HIV drugs (with standard ART or mega-ART) you will need to visit the clinic after 2, 6 and 12 weeks, then every 12 weeks. At all visits you will be examined, be asked to complete a questionnaire about your current health and have blood tests in a fasting state. About 40ml (8 teaspoons) of blood will be taken each time.

If you choose or are allocated to immediately start HIV treatment at trial entry, you will need to visit the clinic 2, 6 and 12 weeks after trial entry, then every 12 weeks. At all these visits you will be examined, be asked to complete a questionnaire about your current health and have blood tests in a fasting state. About 40ml (8 teaspoons) of blood will be taken at each time.

Overall, the study visits are very similar in frequency and duration to those of standard care at your clinic. Your doctor may sometimes wish to see you more frequently for other reasons.

What do I have to do?

You will need to carefully follow the instructions for taking your HIV drugs. All HIV drugs need to be taken regularly. There may be dietary restrictions required for some drugs. You should not use other medications (those on prescription, over-the-counter or illegal) without telling your doctor. People with CD4 cell counts less than 200 are at risk of opportunistic infections and other HIV-related conditions so your doctor will follow the guidelines on prevention (prophylaxis) of these conditions.

What is the drug or procedure that is being tested?

No new HIV drugs are being tested. This is a study to determine if new ways of using the currently available HIV drugs could benefit people for whom several combinations of HIV drugs have failed.

What are the alternatives for treatment?

Other treatments for HIV treatment may be available at your clinic, including licensed and investigational drugs. Your doctor can discuss the advantages and disadvantages of alternative treatment with you. If you

withdraw from the study or fail on the study treatment, your doctor will discuss possible alternative treatments with you.

What are the side effects from treatment received when taking part?

All the available HIV drugs that could be used in the study can cause side-effects and you may experience some of these. If you choose or are allocated to “mega-ART” (a combination of 5 or more HIV drugs) you may have more side effects than on “standard ART” (4 drugs or less). After you enter the trial, or re-start HIV drugs after the drug free period, it is likely that some of your HIV drugs will be different from the ones that you were taking previously and new side-effects could occur. Your doctor will discuss the details of these possible reactions as your treatment is decided. If you experience what could be a side effect, you should tell your clinic doctor at the next clinic visit. If you are worried you should contact the clinic immediately using the emergency number given.

What are the possible disadvantages and risks of taking part?

The study requires you to have blood tests. It may be necessary to insert a needle into your vein more than once if blood does not come out the first time. Blood tests may be painful and cause bruising at the place on your arm where the blood is taken.

You will already have a relatively low CD4 cell count on entering this study and there is a risk that your HIV disease could progress. However, your doctor and the clinic staff will make every effort to find, prevent and treat any complications that happen. Your doctor will be following your progress closely and will explain any treatment options to you if it becomes necessary.

There may be risks in changing from your current HIV combination even though it is failing. Your current combination might be partly protecting you from more rapid progression of your HIV disease. If you enter the trial, your doctor is likely to recommend a change in your HIV combination (guided by the resistance test) in the hope that further progression can be slowed or halted but it is not known whether this will occur. In addition, there is a risk that you could also develop resistance to the drugs you are changed to after you enter the study.

If you choose or are allocated to an HIV drug free period, your CD4 cell count may fall and/or your viral load may rise more rapidly, or your HIV disease may deteriorate, and you could be advised to re-start HIV drugs early. To help you and your doctor decide, the CD4 cell count and viral load will be done 6 weeks after you enter the trial and start the HIV drug free period.

If you choose or are allocated to “mega-ART” (a combination of 5 or more HIV drugs), you may be more likely to reach a lower viral load but this may be short-lived if resistance develops or side-effects limit you taking some of the HIV drugs.

If you choose or are allocated to “standard ART” (up to 4 drugs), you may be less likely to have a fall in your viral load. Your doctor will use the resistance test result to select the HIV drugs most likely to be effective. It is possible, but unproven, that HIV which is resistant to some HIV drugs is less able to multiply so that the treatment may be still partly beneficial.

It is possible that HIV treatment given to a pregnant woman will harm the unborn child. Pregnant women, or women who plan to become pregnant, should not enter this study. A pregnancy test will be done on a urine sample at screening. Women who could become pregnant must use an effective contraceptive during the study. Any woman who finds that she has become pregnant while taking HIV drugs should immediately tell her clinic doctor. If a woman becomes pregnant or breastfeeds during the trial, her doctor will follow the advice of the manufacturer in determining whether particular drugs should be continued.

What are the possible benefits of taking part?

Changing your HIV drug combination based on the results of the resistance test at screening may lead to a better treatment response compared to before you entered the trial. Having an HIV drug free period may allow most of your HIV to become sensitive to HIV drugs again so that on re-starting HIV treatment you get a better response, such as a more sustained rise the CD4 cell count or fall in the viral load. “Mega-ART” may be more effective than “standard ART” if the drug combination contains more HIV drugs that are active against your HIV. However, none of these can be guaranteed. The information we get from this study may help us treat patients with HIV infection better in the future.

What if new information becomes available?

Sometimes during the course of a study, new information becomes available about the strategy that is being tested. If this happens, your doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your doctor will arrange for your care to continue. If you are formally asked to read a new patient information sheet and decide whether to continue in the study you will be asked to sign a new consent form.

What happens when the study stops?

If the study is closed early the reasons for it will be explained to you. After the trial stops, all the HIV drugs that could be used in this study will still be available provided they are licensed or, for unlicensed drugs, they may still be available in expanded access programmes or named patient schemes. Your doctor will recommend an HIV treatment to take.

What if something goes wrong?

If you are harmed as a result of your participation in this study due to someone’s negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you. Your hospital continues to have a duty of care to you as a patient being treated within the hospital whether in a study or not.

If you are harmed and as a result of your participation in this study, and if this is not due to negligence, the Medical Research Council accepts the liability attached to its sponsorship of the study and would sympathetically consider any claim for compensation.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the study will be kept strictly confidential. When you consent to take part in this study you must agree to allow authorised staff from the Medical Research Council (MRC) Clinical Trials Unit or a regulatory authority to inspect your medical records to monitor the study. In no circumstances will your name be disclosed outside the clinic.

We would like you to let us tell your GP that you have entered this study. Also, we will seek your agreement to be able to telephone you or your family if you miss clinic visits or we are concerned about your health. However, if you decline to do so this will be respected and you can still join the study.

Any blood that is being collected from you and frozen in storage may be used at the end of the trial for tests on the HIV it contains. These tests would only look at characteristics of HIV, such as resistance to HIV drugs, which could help explain the results of the trial and contribute to our knowledge of HIV infection. This blood will be stored without any personal identifiers at a central laboratory. By signing the consent form you are authorising the use of this blood for these future tests.

What will happen to the results of the study?

A summary of the results will be released soon after the trial closes and a report submitted for publication. Your doctor will receive copies of these reports.

Who is organising and funding the research?

In the UK, the Medical Research Council (MRC) is funding the trial. Similar government agencies are funding the trial in Canada and the USA.

Who has reviewed the study?

The study has been reviewed by the appropriate Research Ethics Committee covering your hospital.

Contact for further information

The doctor and research nurse conducting this study at your clinic can discuss it in more detail with you and answer any questions. At your clinic these people are:

Doctor:.....Telephone:.....

Nurse:.....Telephone:

