PARTICIPANT INFORMATION AND INFORMED CONSENT

STUDY TITLE:

Zidovudine, lamivudine and dolutegravir (AXD) Relative to tenofovir, lamivudine and dolutegravir (TXD) in Second Line Antiretroviral Therapy (ART) (ARTIST) Trial: a randomised controlled trial

Implemented by the University of Cape Town and Medecins Sans Frontieres
Core study team: Prof. Graeme Meintjies, Dr Claire Keene, Prof Gary Maartens, Ms Tali Cassidy, Dr Tracy Flowers, Dr Paola Lopez, Dr Rulan Griesel and Dr Andrew Hill

Introduction

You are invited to take part in this study. You should understand the research before you agree to join the study. This form will explain the reason for the research, what you will need to do, and any risks or benefits. Please read this information carefully.

Taking part in this study is your choice. You are free to leave the study at any time. If you decide not to take part, or to leave the study, your rights will not be affected in any way. You will be treated in the same manner as before at this clinic and other health care facilities now and in the future.

About the study

Patients who are infected with HIV (the "Human Immunodeficiency Virus") can be treated and kept healthy by taking medicine called antiretroviral treatment (ARVs) every day, which is usually a combination of three different types of ARVs. Each one of these ARVs treats HIV in a slightly different manner to avoid the virus becoming resistant to one of the drugs on its own. Resistance to one or more ARVs may cause the medicine to become ineffective. Different ARVs can be combined into single tablets to decrease the amount of pills a patient must take. In South Africa the first choice (or first line) of ARVs is a single daily pill fixed dose combination (FDC) of tenofovir disoproxil fumarate, emtricitabine, and efavirenz; the combination of all three can be abbreviated as "TEE". HIV can easily become resistant to TEE if someone takes their ARVs irregularly, and their treatment must then be changed to second line ARVs. This includes a combination tablet of zidovudine and lamivudine (which is almost exactly the same as emtricitabine) taken twice daily, as well as lopinavir/ritonavir (known as Aluvia). Lopinavir/ritonavir is taken as two tablets twice daily, and often causes unpleasant side-effects like diarrhoea.

A new ARV called dolutegravir has much less chance of causing side-effects than lopinavir/ritonavir, and acts faster to suppress (decrease to almost zero) the level of HIV (viral load) in the blood. Therefore, patients who need to switch to second line ARVs could potentially get a single dolutegravir pill (instead of lopinavir/ritonavir) once daily, along with the twice daily tablet containing zidovudine and lamivudine (the combination of the three is abbreviated "ALD"). Zidovudine is given as part of second line treatment because HIV often becomes resistant to

tenofovir when a person takes their first line treatment irregularly. Zidovudine may also commonly cause side-effects like nausea and low blood cell counts.

Recent studies have shown, however, that if a person gets dolutegravir as part of their second line treatment, it might be possible to avoid having to take zidovudine by continuing with tenofovir, even if HIV has become resistant to it. The advantages are fewer side-effects, and the fact that there is a fixed dose combination tablet available containing tenofovir, lamivudine and dolutegravir (abbreviated "TLD"), which only has to be taken once daily.

Why is this study being done?

This study will test if the TLD combination tablet is effective to suppress the HIV viral load in a patient who is switched from first line to second line ARV treatment. The ALD combination is currently recommended by the World Health Organization as the best regimen for patients who need second-line treatment. This study won't be able to definitely say whether the TLD combination is better than ALD, but if the study results show that these two treatments are similarly effective, our study may help other researchers with further studies. It may also inform policy-makers in developing guidelines in South Africa and other parts of the world.

Why are you being asked to take part?

You have been invited to take part in this study because you have a HIV viral load (VL) > 1000 copies / ml, and a previous VL > 1000 copies / ml in the past two years, which means that the HIV in your blood is not responding to first line ARVs and may have become resistant to them. You need to start on second line ARVs, and this study will provide you with the chance to use new medications that was not available previously, for the duration of the study period.

What happens in this research study?

During the first stage of the study, up to 65 patients will be started on the fixed dose combination TLD once daily, with an extra tablet of dolutegravir at night for the first two weeks of the study. Thereafter they will receive a single dose of TLD daily. During the second stage, patients will be randomly selected to receive either a single dose of TLD daily, or ALD, which includes one dolutegravir tablet in the morning and another tablet containing zidovudine and lamivudine twice daily. The term "randomly" means that the decision is made similarly to flipping a coin. This is how a randomised controlled trial is done and it is the best scientific way to find out whether a treatment is beneficial or not. The reason for the extra dolutegravir dose during the first stage is to find out if it is necessary to include this additional dose for the first two weeks to get adequate blood levels of dolutegravir in order to reduce the HIV viral load in blood. Up to 195 people will be part of this study in total.

How long will the study last?

You will remain enrolled in the study for 48 weeks, after which you will be transferred back to your normal ARV clinic. The type of ARVs that you must continue with will either be the standard second line treatment given to most patients in the country, or another specialised regimen (medication combination), depending on the results of your blood tests during the study.

What will happen if you decide to take part in the study?

If you want to take part in the study, the study doctor/nurse will discuss the reason for the study with you, what will happen during the study, and your risks, rights and study obligations.

If you agree to take part, you will need to sign the consent form at the end of this document. Once you have signed the consent form, the study team will check whether it is safe for you to be on the study (screening). If eligible you will be enrolled and assigned one of the treatment options mentioned above. After that there will be frequent follow-up visits every 4 weeks until week 24, and again at week 36 and 48. At every follow-up visit we will do a brief exam of your body and assess if there are any side-effects from the treatment you are on. Blood tests will be performed at weeks 4, 8, 12, 16, 20, 24, 36 and 48. See box 1: study schedule for more detail.

Screening: The study doctor will review your medical records, ask you about your medical history and current health, ask you about substances you are using, and examine your body. Your contact details will also be taken in case we need to call you or text you, or do a home visit at a later date. Your blood (15ml or 3 teaspoons) will be tested:

- To check how well your liver and kidneys are working
- To test if you are pregnant (if you are capable of becoming pregnant)
- To measure your CD4 count
- To measure your HIV viral load

Suitability:

In order to take part in the study you need to:

- Be 18 years or older
- Clinically stable
- Have a current HIV VL > 1000 copies / ml and a HIV VL > 1000 copies / ml in the past 2 years (at least 2 months before the current VL)
- Have a CD4 count > 100 cells/µl
- If you are a woman and there is any possibility of you becoming pregnant during the study you must be willing to be on effective family planning (contraception, i.e. “the Pill” or “injection” or implant or intrauterine contraceptive device (IUCD)).

You will not be able to take part:

- If you are pregnant or breastfeeding, or would like to become pregnant in the next 1 year
- If your blood tests are not normal
- If you are allergic or intolerant to any of the study medicines
- If you are on any other medicine that may influence the drug level of dolutegravir
- If you have any mental illness
- If you are using recreational drugs (i.e. Tik, dagga, Mandrax, Unga, cocaine, heroin, etc.) or drinking large amounts of alcohol
- If you are suspected of having, or being treated for active tuberculosis (TB)
- If you are being treated for any serious AIDS related disease (discuss with the doctor or nurse if you are not sure if you have this)
- If you have cancer or have had cancer before
- If you are unable to attend study visits
- If the study doctor thinks that it is best for you not to be on the study.

Enrolment: If the screening finds that you are suitable for the study, we will contact you (by telephone call, sms, whatsapp or home visits) to confirm your participation. We will make an appointment for the first study visit (which should be on the same day that you are switched to your second line ARV treatment). You will be reminded of things you need to do and the things that you cannot do whilst taking part in the study. The study visits will take place at the clinic you are enrolled from.

We will also access your routine clinical data, such as laboratory results, medication prescriptions, appointments and clinic encounters and previous diagnoses on electronic databases.

If you miss an appointment we will send you a text message the next day and if you do not return to the clinic we will call you on the phone.

The order and timing of the study visits is shown in box 1:

<table>
<tr><th colspan="4">BOX 1: STUDY SCHEDULE</th></tr>
<tr><th>Time</th><th>Visit type</th><th colspan="2">Description</th></tr>
<tr><td>Appointment before enrolment</td><td>Screening</td><td colspan="2">This visit will take place at the clinic you are attending (Michael Mapongwana CHC or Ubuntu Clinic). Your contact details and address will be noted. The study team will ask you about your health, other medicines you are taking, and do a physical examination. They will also ask you about your medical history and any previous diagnoses, and will do a screening questionnaire about substances you might be using, called the Audit C. The study team will also take blood (15ml or 3 tablespoons) to check your kidneys and liver function, CD4 count, and test for pregnancy (if you are a woman of child-bearing age).* We will make sure that you meet all the conditions to be part of the study and have none of the conditions that would mean that you cannot take part in the study. You will be given a study appointment calendar outlining the dates and times of your scheduled study visits. Please bring all your regular medicines with you to the next study visit.</td></tr>
<tr><td rowspan="2">Day 0</td><td rowspan="2">Enrolment and start of treatment</td><td colspan="2">We will make sure that you meet all the conditions to be part of the study and have none of the conditions that would mean that you cannot take part in the study. The study doctor will do a brief physical exam and blood (15ml or 3 teaspoons) will be taken for HIV viral load and urine taken to test for pregnancy (if you are a woman of child-bearing age).</td></tr>
<tr><td>Stage 1 (first 65 patients):
You will receive the fixed dose combination of TLD in the morning and an extra tablet of dolutegravir at night for two weeks. Thereafter you will receive the fixed dose combination of TLD daily.</td><td>Stage 2 (all subsequent patients)
You will receive either the fixed dose combination of TLD once daily, or the second line treatment of ALD, which includes one dolutegravir tablet daily and a combination tablet of zidovudine and lamivudine twice daily.</td></tr>
</table>

		We will also take a blood sample (5ml or 1 teaspoon) to do HIV genotyping (testing the genes of the virus for any changes, also called mutations). This test will only be done at the end of the study to test whether the virus was resistant to any of the ARVs before you started ARVs in the study. If your viral load is high during the study, we will take another sample of blood to test the genotype again. This will help doctors to plan for future treatment (see below under "What are the risks of taking part?"). The first 12 patients in each group will also have blood drawn for the levels of dolutegravir and efavirenz in the blood Your contact details and address will be checked
Week 4	Follow-up visit	This will be a follow-up visit where the study doctor will do a brief physical exam and take a history about any side-effects of the treatment you are taking. Blood (15ml or 3 teaspoons) will be taken for kidney function and HIV viral load and urine taken to test for pregnancy (if you are a woman of child-bearing age). Your contact details and address will be checked
Week 8	Follow-up visit	This will be a follow-up visit where the study doctor will do a brief physical exam and take a history about any side-effects of the treatment you are taking. Blood (15ml or 3 teaspoons) will be taken for HIV viral load and urine taken to test for pregnancy (if you are a woman of child-bearing age). Your contact details and address will be checked
Week 12	Follow-up visit	This will be a follow-up visit where the study doctor will do a brief physical exam and take a history about any side-effects of the treatment you are taking. Blood (15ml or 3 teaspoons) will be taken for HIV viral load and urine taken to test for pregnancy (if you are a woman of child-bearing age). Your contact details and address will be checked
Week 16	Follow-up visit	This will be a follow-up visit where the study doctor will do a brief physical exam and take a history about any side-effects of the treatment you are taking. Blood (15ml or 3 teaspoons) will be taken for kidney function and HIV viral load and urine taken to test for pregnancy (if you are a woman of child-bearing age). Your contact details and address will be checked
Week 20	Follow-up visit	This will be a follow-up visit where the study doctor will do a brief physical exam and take a history about any side-effects of the treatment you are taking. Blood (15ml or 3 teaspoons) will be taken for HIV viral load and urine taken to test for pregnancy (if you are a woman of child-bearing age). Your contact details and address will be checked
Week 24	Follow-up visit	This will be a follow-up visit where the study doctor will do a brief physical exam and take a history about any side-effects of the treatment you are taking. Blood (15ml or 3 teaspoons) will be taken for HIV viral load and urine taken to test for pregnancy (if you are a woman of child-bearing age).

		Your contact details and address will be checked
Week 36	Follow-up visit	This will be a follow-up visit where the study doctor will do a brief physical exam and take a history about any side-effects of the treatment you are taking. Blood (15ml or 3 teaspoons) will be taken for HIV viral load and urine taken to test for pregnancy (if you are a woman of child-bearing age). Your contact details and address will be checked
Week 48	Follow-up visit	The study team will ask you about your health and do a physical examination. The study team will also take blood (15ml or 3 tablespoons) to check your kidney function, your HIV viral load, CD4 count, and urine taken to test for pregnancy (if you are a woman of child-bearing age). Your contact details and address will be checked

Blood will also be taken at certain visits and stored to allow measurement of the levels of ARV drugs in your blood after you have completed the trial.

What are the risks of taking part?

The study medicines: Most people treated with these medicines do not experience bad side-effects. However, the study medicines can cause bad side-effects that you should know about. If you think you might be suffering from a bad side-effect of the medicines at any time during the study, you need to report this to the study doctor (or any other study team member) immediately.

Dolutegravir may cause diarrhoea, nausea, abdominal pain and/or vomiting, as well as dizziness and headaches. It may also cause difficulty with sleep and unusual dreams and can make you feel anxious, unable to concentrate or depressed. Rarely it can cause severe liver damage and/or skin reactions.

Tenofovir may cause problems with kidney function in a small amount of people. People with kidney problems should not take this ARV. If your first blood results show that your kidney function is normal, however, it should be safe for you to continue with this treatment. We will monitor your kidney function after month 1, 4, and 12, and we will not give it to you if it looks like it is causing any problems with your kidneys and will change it to an alternative ARV. If any problem does occur, this usually improves when the medication is stopped.

Zidovudine may cause nausea, vomiting, and low blood counts in some people. In stage 2, we will monitor your blood counts (haemoglobin, white cell count and platelets) at the first visit, months 1, 2, 3 and 6. If these results are abnormal you may be switched to a different ARV.

Lamivudine may cause low red blood counts in a very small number of patients. We will monitor for this based on symptoms and during physical examinations. If this occurs you may be switched to a different ARV.

When HIV is not responding to first line treatment anymore, there is a high likelihood of it being resistant to treatment as a result of various changes in the virus (mutations). It is difficult to say if resistance to tenofovir might make it more likely to get resistance to dolutegravir if it is given with

tenofovir. Being on TLD as second line ART might increase the risk of you developing ARV resistance or it might not – that is one of the questions we are planning to answer in this study. There is a small chance that you may develop resistance to the ARV treatment you are given in this study whatever treatment you receive (the ARV medicines will not work as well as they should, because your HIV has found a way to escape their action). We will test your HIV viral load frequently, and if it is not adequately decreased when it should be, we will perform a special test on the HIV in your stored blood (from before you started the ARV treatment) and the HIV in a current blood sample. This will be to see if the HIV has become resistant to the ARVs you are using and which new ARVs we can prescribe to you that will work effectively.

Risks of taking blood samples. You may have discomfort and mild pain with blood taking (insertion of a needle into your vein). You might have mild bruising. However, as the study staff are experienced, these effects should be minimal. The total amount of blood taken during the study will not exceed a 100 ml of blood. This is less than ½ a cup and far less than the amount of blood drawn at a single blood donation.

Safety monitoring. To monitor the safety of the study treatments we will ask you at each study visit about your health and about any problems that could be caused by the medicines. We will also take regular blood to test your kidney function, and monitor your HIV viral load. If you are worried about a change in your condition, you should contact the study team urgently.

Risk to pregnancy and unborn child. We do not want you to be pregnant before you enter the study or become pregnant during your time enrolled in this study. A recent study has shown that a small percentage of children born to women who became pregnant while using dolutegravir, were found to have neural tube defects. Neural tube defects are birth defects of the brain, spine, or spinal cord. They happen in the first trimester of pregnancy, often before a woman even knows that she is pregnant. This safety signal is not yet confirmed, but we are still concerned about it and want you to be aware of it.

Some of the benefits of taking dolutegravir are that it has fewer side effects and you only have to take it once a day compared to the other option for second-line called lopinavir/ritonavir (sometimes called Aluvia). The risk of these neural tube defects when taking dolutegravir is low: less than 1% of pregnancies. The risk on dolutegravir that was found was 0.94% of pregnancies, compared to 0.12% without dolutegravir. It is your decision to balance these risks against the potential benefits of taking dolutegravir as your treatment.

However, for this reason, if you are a woman who is capable of becoming pregnant and would like to take part in this study, we do emphasise that you must be using an effective method of contraception to avoid becoming pregnant for the duration of the study. We will talk with you about contraception options and help you choose the best method for you at each visit. Your birth control method must be one that is considered effective: a hormonal injection, oral contraceptive, implant or an intrauterine contraceptive device. This can be provided by your usual clinic. In this way the study doctor knows that you are consistently using an effective birth control method and the chance of you becoming pregnant during the study is reduced.

It is important that you inform the study doctor or study team whenever you change your pregnancy

intentions. If you have decided to fall pregnant or become pregnant during the study, the study medication including dolutegravir will be stopped and you will be changed to alternative ARV medication. We will monitor your progress and follow up on the outcome of your pregnancy.

What are the possible benefits of taking part?

Aside from the possibility of receiving a treatment regimen (combination of treatments) that is only one pill a day and might prove to have fewer side-effects than the standard treatments, you will not benefit directly from taking part in the study. The results of the study may benefit future patients with HIV who need to be switched to second line ARVs, and may be able to take a single pill containing TLD instead of a multi-pill regimen of ALD or other medication. We will inform your clinic doctor of the results of the tests performed at the screening and last study visits. This information will help your doctor to adjust your management appropriately when you resume your normal appointments at your ARV clinic.

How will the information and samples collected in the study be handled and stored?

Information will be recorded by the study staff on case report forms, which will be captured and uploaded into a study database. The data will be stored on a password protected hard drive, kept at the University of Cape Town. These records will be kept for ten years after the end of the trial.

Blood samples will be taken and sent to the National Health Laboratory Service for the tests explained above. A small amount of blood will be stored for tests of dolutegravir levels at a later date in the study. Blood samples will be kept for ten years after the end of the trial.

If in future, you decide that you do not wish for your samples to be stored anymore, you can contact the researchers or the UCT ethics committees and inform them of your decision. Your samples will then be destroyed and no further tests will be done on them

Use of the information for other studies

Other researchers may apply to University of Cape Town Human Research Ethics Committee for permission to use the information we gather or the samples we store for other studies. Further tests on these samples and further analysis of the information will only be performed if the ethics committee agrees and grants this permission. The information and samples will not be linked to your name so any further research will not have access to your identity.

When you sign the consent below, your permission to store your samples and use them for future testing will be asked as a separate question for you to agree to. You are free to decline the request to store your samples for future testing and still participate in this study.

Will your privacy be protected?

All patient interactions will maintain strict confidentiality. To protect your identity, all information and all samples collected will be labelled with a study code. This code (and not your name) will be used for all study data and samples. Your medical records and the information collected for the study will be looked at by authorised persons from the study team. Your records may be reviewed by the

research ethics committee overseeing the study, the South African Health Products Regulatory Authority, the funders who have authority to check that the study is being carried out correctly, or by an independent committee of doctors who will be making sure that the study is safe. All persons will treat any information about you as a research participant confidentially, and nothing that could reveal your identity will be disclosed outside the research site.

What if 'Something Goes Wrong'?

This research study is covered by an insurance policy taken out by the University of Cape Town if you suffer a bodily injury because you are taking part in the study. The insurer will pay for all reasonable medical costs required to treat your bodily injury, according to the SA Good Clinical Practice Guidelines 2006, which are based on the Association of the British Pharmaceutical Industry Guidelines.

The insurer will pay without you having to prove that the research was responsible for your bodily injury. You may ask the study doctor for a copy of these guidelines. The insurer will not pay for harm if, during the study, you:

- Use medicines or other substances that are not allowed
- Do not follow the study doctor's instructions
- Do not tell the study doctor that you have a bad side effect from the study medicine
- Do not take reasonable care of yourself and your study medicine.

If you are harmed and the insurer pays for the necessary medical costs, usually you will be asked to accept that insurance payment as full settlement of the claim for medical costs. However, accepting this offer of insurance cover does not mean you give up your right to make a separate claim for other losses based on negligence, in a South African court.

You must notify the study doctor immediately of any side effects and/or injuries during the study, whether they are research-related or not.

Will you be compensated for your travel costs, time and inconvenience?

You will be compensated for your time, inconvenience and transport expenses for each scheduled visit (R250 per visit). Unscheduled visits will not be compensated unless the study team requests you to return for an appointment.

Who is managing this study?

This study is sponsored by the University of Cape Town, who are responsible for maintaining the quality of the trial and ensuring that the trial is conducted in compliance with the protocol, good clinical practice and regulatory requirements. The trial is funded by a grant from the Wellcome Trust and by Medecins Sans Frontieres (MSF). There are no potential conflicts of interest for any of the researchers or organisations sponsoring, funding, supporting or involved with the study in any way

What will happen with the results of the research?

The results of the study will be published so that they are available to the medical profession throughout the world. No patients will be identified individually.

Withdrawal from the study

You have the right to stop taking part in the study at any time. If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them as soon as possible. The investigator may decide to stop your participation without your permission because he/she may decide that staying in the study will be bad for you. If one of the study medicines causes you harm, you will be withdrawn from the study and your treatment changed to an alternative. If you withdraw early, the study team will encourage you to continue to be followed up by the study team, but it is your right to decide. You will be referred back to your local primary health clinic to continue your treatment if you choose not to be followed up by the study team.

What if you have complaints about the study?

The ethical oversight of this study is performed by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee. If you want any information regarding your rights as a research participant, or have complaints regarding this research, you may contact: your doctor or the Ethics committee, by contacting:

Prof. Marc Blockman, the Chairperson of the Research Ethics Committee at the University of Cape Town (telephone: 021 406 6338)

After you have consulted your doctor or the Ethics Cmmittee, and if they have not provided you with answers to your satisfaction, you should write to the South African Health Products Regulatory Authority (SAHPRA) at:

The Registrar
South African Health Products Regulatory Authority (SAHPRA)
Department of Health
Private Bag X828
Pretoria
0001

Contacting the study team

If you experience any worrying effects on the study treatment, please contact the study team as soon as possible. If you or your health care provider have important questions or concerns, please contact the study team.

You can contact the study nurse or doctor [*contact details to be added before recruitment starts*]. You can also send a please call me and we will call you back.

If you have general questions about the study you can also contact the Principal Investigators: Dr Claire Keene (telephone: 021 364 5490) or Prof Graeme Meintjes (telephone: 021 406 6075).

Statements of agreement and signatures

1.	I have read the information pages about the study, or they have been read to me. I understand the advantages and disadvantages, as well as the benefits and risks, of taking part in the study. The details of the study have been explained to me and my questions have been addressed. I will

	receive a copy of this signed consent form.

2.	I understand that participation in the study will involve: • Tests including physical examination and questionnaires, and collection of blood samples • Taking doses of the ARV medicines, fixed dose combination TLD with or without added dolutegravir, or a multi-pill regimen of ALD • There might be or might not be an increased risk of developing ARV resistance if TLD is taken as second line ARV treatment • Attending the study visits and taking of blood samples for safety tests and measurements of the blood ARV levels • If I am a woman capable of becoming pregnant that I will be on effective contraception throughout the study, and if I wish to become pregnant I will inform the study doctor before doing so. • The study team and the clinic staff may contact me by telephone, text messages, whatsapp or home visits

3.	I understand that I can withdraw permission to take part and leave the study at any time, without having to give a reason, and without affecting my normal care and treatment.

4.	I understand that the information will be reviewed by authorised individuals and that the individuals are obliged to treat the information as confidential.

5.	I agree to take part in the study.

PLEASE INITIAL/MARK THE BOX IF YOU AGREE

6.	I agree to have blood samples stored. These will be used to test to see what ARVs the virus is resistant to and to test levels of ARVs in my blood. This could help doctors to plan for future treatment if the current ARVs are no longer working.	

7.	I agree to have blood samples stored after the study has been completed. Other tests related to HIV may be performed on these samples in the future if the UCT Human Research Ethics Committee agrees to this.	

Participant's signature	Given (first & middle) names – please print
	Surname (last/family) name – please print
	Date: D D M O N 2 0 Y Y

Witness signature (if applicable)	Name – please print	Date
		D D M O N 2 0 Y Y

Responsible study team member's signature	Name – please print	Date
		D D M O N 2 0 Y Y

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Zidovudine, lamivudine and dolutegravir (AXD) Relative to tenofovir, lamivudine and dolutegravir (TXD) in Second Line Antiretroviral Therapy (ART) (ARTIST) Trial: a randomised controlled trial

GENETIC TESTING
INFORMED CONSENT FORM

This is a separate consent form requesting your permission to do genetic tests on your blood sample. Permission for this is entirely voluntary and if you do not agree to have a sample taken, stored and used for genetic testing, you can still take part in the ARTIST trial.

Genes:
Genes are codes in your body cells that make up your individual features, including how your body reacts to and handles (metabolizes) medication once it is in your body.

Purpose of genetic testing and what type of genetic studies may be done:
If you agree to have a sample taken for genetic testing then this sample would involve us taking an extra 5 ml (one teaspoon of your blood) and storing this sample.. Future studies would then use this sample to do tests in order to investigate how your genes are associated with your body's response to HIV infection and how your genes influence the way your body reacts to and handles (metabolises) medication once it is in your body.

No tests will be done for genetic diseases or any other conditions not related to HIV infection. This information will not influence decisions about treatment for your illness now and results will not be given to you.

Where genetic testing will be done:
Your samples will be stored and tested in Cape Town. Genetic studies will be carried out at the University of Cape Town, but when the test is not available at UCT the sample may be shared with a collaborating university if there are tests that cannot be done in Cape Town, so samples may be shipped to other countries to research colleagues for further testing. Shipping samples would need permission from the University of Cape Town Ethics Committee.

Confidentiality:
Your name will not appear on any research sample, only a study number. All personal data that may link your identity to the sample will be stored in a secure location. Nothing will appear on the sample that could link your identity to the sample, whether genetic testing is done locally or shipped to another country. If researchers need to know any details about your illness it will be shared with them anonymously, i.e. your name will not appear on the information.

Ownership of samples:
If you allow us to store your sample it means you are giving your sample to us. The sample will be under the responsibility of Prof Graeme Meintjes at the University of Cape Town. The sample may be shared with other researchers if their help is needed with testing. They will not be sold. The samples will be stored indefinitely, unless you tell us to destroy them.

Approval for genetic testing:
Before any genetic testing will be done on the sample, permission will be requested from the University of Cape Town Human Research Ethics Committee for the specific testing that will be done.

GENETIC TESTING
INFORMED CONSENT FORM

Access to the genetic data or the sample will be granted by this Research Ethics Committee after reviewing the applicant's request in detail, provided that the request complies with research principles and the purpose of the genetic testing set out above.
Genetic data may be shared with other researchers in publications, but no identifying information will be shared and it will not be possible to link the genetic data to individual patients.

You confirm that the following has been explained to you, and you have had a chance to ask questions:

1. Genes are codes in your cells that code for your individual features.
2. We want to store a sample of your blood for genetic testing.
3. These tests will only relate to your current illness and your body's response to HIV and handling of HIV medication.
4. These tests will not influence your treatment and you will not get the results.
5. The samples will be stored and tested in Cape Town, unless the tests cannot be done in Cape Town, in which case it may be shipped to other countries for testing.
6. Samples and information related to your illness will be anonymised when stored and tested.
7. Approval will be obtained from the University of Cape Town Ethics Committee before any genetic tests will be done on your sample.
8. If you decide not to give permission for genetic testing this will not influence your participation in the trial in any way.

Contacts and Questions:
You may ask any questions you have now. If you have questions later, you are encouraged to contact: Dr Claire Keene on phone number 021 364 5490 or Prof Graeme Meintjes on phone number 021 406 6075.

In case of any questions regarding the welfare and rights of research participants, you should contact the UCT Research Ethics Committee at 021 406 6492.

Consent
I have read the above / the above has been read to me, and I have had the opportunity to discuss genetic testing with _____ and ask any questions.

☐ I agree to storage and genetic testing of my samples

☐ I do NOT agree to storage and genetic testing of my samples
∗ If this is ticked then no samples will be taken for genetic testing during the course of the study.

OR Thumb Print

STUDY TITLE:
Zidovudine, lamivudine and dolutegravir (AXD) Relative to tenofovir, lamivudine and dolutegravir (TXD) in Second Line Antiretroviral Therapy (ART) (ARTIST) Trial: a randomised controlled trial

GENETIC TESTING
INFORMED CONSENT FORM

Participant Name (Printed) _____

Participant Signature _____

Date signed _____

SIGNATURE OF INDEPENDENT WITNESS:

(If participant is unable to read/write) _____

Name of witness (Printed) _____

Date signed _____

PERSON ADMINISTERING INFORMED CONSENT:
I confirm that the participant signing consent above had enough time to consider this information, had an opportunity to ask questions, and voluntarily agreed to participation in the study.

Signature of person who administered informed consent _____

Name of person who administered informed consent (Printed) _____

Date signed _____

PHARMACOKINETIC SUB-STUDY
PARTICIPANT INFORMATION AND INFORMED CONSENT

STUDY TITLE: Zidovudine, lamivudine and dolutegravir (AXD) Relative to tenofovir, lamivudine and dolutegravir (TXD) in Second Line Antiretroviral Therapy (ART) (ARTIST) Trial: a randomised controlled trial

Implemented by the University of Cape Town and Médecins Sans Frontières.
Core study team: Prof. Graeme Meintjes, Dr Claire Keene, Prof Gary Maartens, Ms Tali Cassidy, Dr Tracy Flowers, Dr Paola Lopez, Dr Rulan Griesel, and Dr Andrew Hill.

Introduction

You are invited to take part in this sub-study (a smaller part of the main ARTIST study). You should understand the research before you agree to join the sub-study. This form will explain the reason for the research, what you will need to do, and any risks or benefits. Please read this information carefully.

Your study doctor has already established that you are a suitable patient to take part in the ARTIST clinical trial. You're now invited to take part in an additional sub-study, the aim of which is to collect more blood samples to measure the levels of the medicines in your blood.

Taking part in this study is your choice. You are free to leave the study at any time. If you decide not to take part, or to leave the study, your rights will not be affected in any way. You will be treated in the same manner as before at this clinic and other health care facilities now and in the future.

Why are you invited?

You are invited to take part in the sub-study because you have already agreed to take part in the ARTIST study, where you will be given study medicines, undergo medical examinations and procedures at scheduled visits. In the sub-study we ask for permission to take more blood samples at specific times. Twelve participants from the first stage of the study, and 12 participants from the second stage of the study will be enrolled into the sub-study. You will only be invited to take part if you are using the tenofovir, lamivudine and dolutegravir (abbreviated "TLD") fixed drug combination tablet. Your choice to take part in this optional sub-study does not affect your participation in the ARTIST study.

Why is this sub-study being done?

We will be taking blood samples from you for efavirenz and dolutegravir levels. There is a drug-drug interaction between these two drugs: efavirenz causes an increase in the breakdown (metabolism) of dolutegravir in your body which causes dolutegravir levels to be lower in your blood. Even after you have stopped taking efavirenz this effect still continues for about 2 weeks in your body. Because you will be starting dolutegravir immediately after

stopping efavirenz we need check that your dolutegravir blood levels are effective while the increased breakdown effect of efavirenz is still there. The risk is that after stopping efavirenz and not having high enough dolutegravir levels in your blood, HIV can become resistant to dolutegravir. Dolutegravir levels will be measured in your blood just before you take the next dose of it (this is called a trough level and is the best measure of how effective dolutegravir is in your body). We will be trying to see how long it takes for dolutegravir in your blood to reach an effective level. We will also be measuring how long it takes for efavirenz to reach an ineffective level and disappear from your blood after you stop using it.

Genes are codes in your body cells that make up your individual features, including how your body reacts to and metabolises medication. Many people have a genetic 'weakness' that cause them to metabolise efavirenz slower. For this reason we will be testing your genes to see how well you metabolise efavirenz and how that influences your efavirenz and also dolutegravir levels.

What will happen to you if you take part?

You will be asked to sign this form to show that you understand what the sub-study is about and that you agree to take part. Before we include you in the sub-study, we need to make sure you understand the sub-study including what will happen, any possible risks and what is required of you. If you decide to take part, you have to sign the consent form to show your willingness to take part.

We will need to make sure that you take your medication every day while you are enrolled into the sub-study. For this reason, we will be supplying you with an electronic tablet container (Wise Pill®). It will notify us when you open the container to take your tablets. If you do not open it, we will also know. We will be sending you an sms to remind you to take your medication every day.

For the sub-study, we will be taking a blood sample on the day that you stop using efavirenz and start using dolutegravir. This will be a 5 mL (one tablespoon) sample of blood. At that time, we will also be taking a blood sample for the genetic testing, this will be another 5 mL (one tablespoon) of blood.

To ensure that we get a trough blood level for the dolutegravir, we will ask you to take the tablet of TLD in the morning at 9am while you are enrolled in the sub-study. You will be

asked to come in on days 3, 7, 14, and 28 after you start using the TLD. On these days, you must please ***NOT*** take the TLD tablet before coming to the clinic. At the appointments we will take 2 x 5 mL samples of blood (2 x one teaspoon), and after this you may take your TLD tablet.

Potential benefits

There is no benefit to you from being in this sub-study. Results of these studies are for research purposes only and are not expected to benefit you directly. Therefore, you will not have access to the results. Your taking part may help patients with HIV in the future.

Risks and inconveniences

This is a minimal risk sub-study. The risks of taking blood may include fainting, pain, and/or bruising. For this sub-study, the total amount of blood to be taken from you will be approximately 50 mL (less than a quarter of a cup).

How will the information and samples collected in the study be handled and stored?

Information will be recorded by the study staff on case report forms, which will be captured and uploaded into a study database. The data will be stored on a password protected hard drive, kept at the University of Cape Town. These records will be kept for ten years after the end of the trial.

Blood samples will be taken and sent to the Clinical Pharmacology Laboratory at University of Cape Town for the tests explained above. Blood samples will be kept for ten years after the end of the trial.

Confidentiality

To make sure all information remains confidential, the blood samples will be labelled with study numbers only, and none of the information that could identify you will be put on the samples. Your information will be kept confidential within the limits of the law and used only for research purposes mentioned above. If the results of this study are published or presented in a meeting, you will not be named, and nobody will be able to tell that you were in the study from the publication or presentation.

PHARMACOKINETIC SUB-STUDY
PARTICIPANT INFORMATION AND INFORMED CONSENT

STUDY TITLE: Zidovudine, lamivudine and dolutegravir (AXD) Relative to tenofovir, lamivudine and dolutegravir (TXD) in Second Line Antiretroviral Therapy (ART) (ARTIST) Trial: a randomised controlled trial

Voluntary participation and withdrawal

Taking part in this sub-study is your choice. If you decide not to take part, this will not affect the medical care you receive from your study doctor or the clinic, or your participation in the main study. You are free to leave the sub-study at any time. If you decide to leave the sub-study, your rights will not be affected in any way. You will be treated in the same manner as before at this clinic and other health care facilities now and in the future.

Authorisation to use and disclose records for research

By signing this form you give consent to take part in this sub-study, you are agreeing that the study doctor, the research team, the institution, study monitors/inspectors/auditors, and a central laboratory may use and disclose your information, together with your study subject number, to the Institutional Review Board overseeing this study, and to governmental authorities if appropriate. These uses and disclosures are necessary to conduct the study and to ensure its integrity.

What if 'Something Goes Wrong'?

This research study is covered by an insurance policy taken out by the University of Cape Town if you suffer a bodily injury because you are taking part in the study. The insurer will pay for all reasonable medical costs required to treat your bodily injury, according to the SA Good Clinical Practice Guidelines 2006, which are based on the Association of the British Pharmaceutical Industry Guidelines.

The insurer will pay without you having to prove that the research was responsible for your bodily injury. You may ask the study doctor for a copy of these guidelines. The insurer will not pay for harm if, during the study, you:

- Use medicines or other substances that are not allowed
- Do not follow the study doctor's instructions
- Do not tell the study doctor that you have a bad side effect from the study medicine
- Do not take reasonable care of yourself and your study medicine.

If you are harmed and the insurer pays for the necessary medical costs, usually you will be asked to accept that insurance payment as full settlement of the claim for medical costs. However, accepting this offer of insurance cover does not mean you give up your right to make a separate claim for other losses based on negligence, in a South African court.

STUDY TITLE: Zidovudine, lamivudine and dolutegravir (AXD) Relative to tenofovir, lamivudine and dolutegravir (TXD) in Second Line Antiretroviral Therapy (ART) (ARTIST) Trial: a randomised controlled trial

You must notify the study doctor immediately of any side effects and/or injuries during the study, whether they are research-related or not.

Will you be compensated for your travel costs, time and inconvenience?

You will be compensated for time, inconvenience, and travel. You will receive R250 for each visit that you attend for us to take blood for this sub-study.

Who is managing this study?

This sub-study is sponsored by the University of Cape Town, who are responsible for maintaining the quality of the study and ensuring that the study is conducted in compliance with the protocol, good clinical practice and regulatory requirements. The sub-study is funded by a grant from the Welcome Trust and by Médecins Sans Frontières (MSF). There are no potential conflicts of interest for any of the researchers or organisations sponsoring, funding, supporting or involved with the study in any way.

Ethical approval

- This study protocol has been submitted to the University of Cape Town, Human Research Ethics Committee (HREC) and written approval has been granted by the committee.
- The study has been structured in accordance with the Declaration of Helsinki (last updated: October 2013), which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.

What will happen with the results of the research?

The results of the sub-study will be published so that they are available to the medical profession throughout the world. No patients will be identified individually.

Sources of additional information

For the duration of the study, you will be under the care of qualified medical doctors and nurses. If at any time between your visits, you feel that any of your symptoms are causing you any problems, or you have any questions during the study, please do not hesitate to contact the study staff.

PHARMACOKINETIC SUB-STUDY
PARTICIPANT INFORMATION AND INFORMED CONSENT

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You can contact the study nurse or doctor: [*contact details of study nurse to be added before recruitment starts]* or Dr Rulan Griesel (telephone: 0823197397).

If you have general questions about the sub-study you can also contact the Principal Investigators: Prof Gary Maartens (telephone: 021 406 6286) or Dr Claire Keene (telephone: 021 364 5490) or Prof Graeme Meintjes (telephone: 021 406 6075).

If you want any information regarding your rights as a research participant, or complaints regarding this sub-study, you may contact Prof. Marc Blockman, Chairperson of the University of Cape Town, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants (telephone: 021 405 6338).

You can also contact Dorah Diale at the South African Health Products Regulatory Authority (SAHPRA) (telephone: 060 548 4332).

Informed consent:

1. I hereby confirm that I have been informed by the study staff about the nature, conduct, benefits and risks of the study and have agreed to participate in the sub-study.
2. I have read this document/had its contents explained to me.
3. I have been given the opportunity to ask any questions about the research study procedures.
4. I have been given time to discuss with others to decide whether or not to take part.
5. I understand that blood samples will be taken and will be analysed and I will not have access to the results.
6. It has been explained to me that I am free to leave the sub-study at any time, without any disadvantage to my future care I do freely give my consent to join in this sub-study, as described to me in this document.
7. By signing this consent form I authorise use and sharing of my medical information as described under section “Authorisation to use and disclose records for research” to ensure the study is conducted with integrity. This consent is valid until I revoke it.
8. I understand that I will receive a copy of this document as signed below.

PHARMACOKINETIC SUB-STUDY
PARTICIPANT INFORMATION AND INFORMED CONSENT

STUDY TITLE: Zidovudine, lamivudine and dolutegravir (AXD) Relative to tenofovir, lamivudine and dolutegravir (TXD) in Second Line Antiretroviral Therapy (ART) (ARTIST) Trial: a randomised controlled trial

Participant's signature	Given (first & middle) names – please print									
	Surname (last/family) name – please print									
	Date:	d	d	m	o	n	2	0	y	y

Witness signature (if applicable)	Name – please print	Date								
		d	d	m	o	n	2	0	y	y

Responsible study team member's signature	Name – please print	Date								
		d	d	m	o	n	2	0	y	y