



## Dolutegravir in Pregnant HIV Mothers and Neonates

### Participant Information Sheet

D2 ☐-☐☐☐☐

**Chief Investigator:** Professor Landon Myer

**Site Locations:** Gugulethu Community Health Center, Cape Town

Site contact number: +27 699 8238

#### Introduction

*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.*

#### Why have I been chosen?

You have been chosen because you are pregnant and have recently been diagnosed with HIV, but have not yet started treatment.

#### What is the purpose of the study?

Many women in this country become aware of their HIV status towards the end of pregnancy. This means that the risk of the baby becoming HIV-infected is high because the level of virus (HIV) in the mother's blood is still high by the time of delivery, even with the best available treatment. Current HIV treatments can take up to six months to reduce the levels of HIV virus in the blood (viral load), and so if you start treatment in late pregnancy, the medicines may not have time to fully work by the time your baby is born. Recent studies in adults have shown that with a new drug, dolutegravir, the HIV in the blood can become very low in about 4 weeks, and for this reason it is most important to study the use of dolutegravir in patients who need it most. We do not yet know if this same effect is seen in pregnant women.

Women who present in late pregnancy are a very important group who may benefit from the rapid action of the drug, and this study aims to check if that the drug works in the same way in pregnant women as it does in non-pregnant adults. We want to know whether antiretroviral therapy (ART) which includes dolutegravir is more effective than the current national policy ART in reducing the amount of HIV in the blood of pregnant women by the time of delivery. However, this is the first time that dolutegravir has been studied in this way in pregnant women and we do not know if it will be better than standard antiretroviral treatment or not.

#### 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. You will still be free to withdraw at any time and without giving a reason. This will not affect the standard of care you



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receive. If you do decide to withdraw at a later stage, you will be asked whether you wish for your samples will be removed and destroyed.

### **What will happen to me if I take part?**

It will have been recommended that you start treatment for your HIV as soon as possible, and the clinic will recommend that you start treatment on the same day as you receive your diagnosis, whether or not you decide to take part in the study, since this is standard practice in South Africa. Whilst you need to decide quite quickly because it is important for your health to start treatment the same day, you will be given sufficient time to consider whether you wish to participate in this study. If you choose to take part in this study, you will be enrolled into the study. At each study visit, we will make sure you are still happy to participate in the study.

Once you have been enrolled into the study, you will be selected to (1) either receive the standard treatment -containing Efavirenz or (2) receive the study treatment- containing Dolutegravir. This is done by a computer and this means about half the women will be selected to remain on the standard of care treatment and half will be selected to be treated with the study drug. This means that we will end up with two groups which will enable us to compare the two ways of treatment at the end of the study. You will then be asked to attend follow-up visit at the study clinic approximately ten times. The time you will be enrolled in the study is approximately 21 months.

When you decide to be part of the study, we will also do an ultrasound examination of the baby to assess the baby's growth. Ultrasound is very safe for the baby. Occasionally the scan shows a problem with the baby which might mean that additional medical care is required – we will discuss all results with you, and provide time for you to ask any questions. If it was needed, we will arrange for an appointment with a local specialist. We will also ask whether we can collect a sample of vaginal fluid at the start of the study so that we can tell how much virus is in the birth canal before we start treatment. This is important because we do not know how well either Dolutegravir or the standard HIV treatments reduce the amount of virus the baby will be exposed to during birth.

Regardless of which treatment you receive, you will be asked to come to the research site for the staff to assess you clinically and to draw some blood to check your results after the first week on your treatment. If the blood test result is not normal, you may not be able to remain in the study. If that is the case, we will make sure you get the treatment you need from the ARV clinic. If you had been on Dolutegravir, you will need to switch to the medicine that is provided by your local clinic. If the blood results show a medical problem that needs additional care, we will make referrals to doctors who can do this.

If you remain in the study we will repeat the ultrasound examination, blood tests and vaginal sample after three weeks on treatment. When you go into labour, we will ask you to inform the midwife that you are enrolled in the study, and we will take a blood sample from you and the umbilical cord if possible. We will ask to take a specimen from the placenta. If a member of the study team is not able to attend the delivery, we will arrange to see you and your baby in clinic within 2 weeks of the birth. We will arrange to see you and your baby in our clinic after 6, 12, 24,



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48 and 72 weeks. These visits will involve a clinical check-up for you and the baby and taking some blood samples and samples of your breast milk to make sure that the medication is not causing any bad effects, and to measure the amount of HIV virus in your blood and breast milk. If we find out that your baby has HIV we measure the amount of HIV virus present in baby's blood. At 6 weeks a throat swab and stool swab will be taken from your baby if you gave a vaginal sample before delivering your baby. After you have delivered your baby you may take medication known as contraception to prevent pregnancy. We will ask to take an extra blood sample from you at each visit you are taking contraception and also a sample to check for pregnancy on all study visits from 12 weeks after you give birth.

The study team will be available at all times should you have any side effects or concerns about your health or about the study.

We anticipate that your baby will be weaned around 48 weeks after birth, but we wish to see you both again at 72 weeks for a final visit to make sure that you are both well, to measure your HIV viral load and to perform a final HIV test on the infant. Whilst the results of the study will not yet be available, you will be given the option of continuing on Dolutegravir-based ART (rather than switching to standard of care) for a further 6 months.

#### **What are side effects/ risks of taking part?**

Dolutegravir, the investigational drug, has been studied in both healthy volunteers and patients being treated for HIV. It has been well tolerated and is proven to work well against HIV. However, all medicines carry some risk of side effects, and it is for this reason that we wish to see you eight times during the study to see how you are. Commonly occurring side effects include mild nausea and diarrhoea or headache. It should be noted that similar side effects are noted with other combinations of HIV drugs, including the national policy combination.

The following side effects have been seen with dolutegravir in HIV-infected patients:

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Very Common (Around one person in ten)	Common (Around one person in a hundred)	Uncommon (Around one person in a thousand)
<ul style="list-style-type: none"> <li>• Headache</li> <li>• Feeling sick</li> <li>• Loose stools</li> </ul>	<ul style="list-style-type: none"> <li>• Rash</li> <li>• Itching</li> <li>• Vomiting</li> <li>• Stomach pain</li> <li>• Difficulty in sleeping</li> <li>• Dizziness Abnormal dreams</li> <li>• Lack of energy</li> <li>• Flatulence (gas or wind)</li> <li>• Changes in results of blood tests</li> </ul>	<ul style="list-style-type: none"> <li>• Allergic reaction</li> <li>• Liver problems</li> <li>• As your HIV starts to improve and your body becomes stronger, you are now able to fight off infections. But at first, this can make you feel more unwell, and occasionally can be serious. This is known as IRIS</li> </ul>

Most of the side effects listed above have not been very serious, and have not stopped HIV-infected patients from getting on with their lives as normal. Some side effects, such as allergic reaction, liver problems and IRIS have been severe, but are rare.

### *Severe allergic reaction*

Allergic reactions have been reported with dolutegravir and similar medicines. If you get this, you may feel generally unwell, have a skin rash, a high temperature (fever), lack of energy, swelling sometimes of the face or mouth causing difficulty in breathing, blisters, mouth ulcers, sore eyes and muscle or joint aches.

If you develop any of these signs and symptoms during the study then you must **call your study doctor** immediately, who may decide to carry out tests on your liver, kidneys or blood, and may tell you to stop taking dolutegravir. If your doctor tells you to stop taking study medications because of this type of reaction then you must do this immediately

### *Liver problems*

A small number of HIV-infected patients in other studies with dolutegravir have had problems with their liver in the first few weeks or months of taking the new medicines. These have included some HIV-infected patients receiving HIV treatment for the first time, some who have previously received HIV treatment before and some who have limited HIV treatment options left. Most of these patients were also taking other medications HIV and other conditions which also may cause liver problems, and some of them had liver problems before starting treatment. This is why we will do blood tests before you start the study, and regularly during the study – these will detect any problems with your liver or kidneys quickly.



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### *Potential neurological development problems in the baby*

One new study in mothers taking dolutegravir when they get pregnant or in the first three months of pregnancy, showed a very small increase in babies having problems with neurological development. These results are still under evaluation. We cannot tell for sure that dolutegravir causes these problems.

If you are asked to take part in DolPHIN 2 it means you are 28 weeks pregnant or more. Results for starting dolutegravir treatment in this late stage of pregnancy show there is no increased risk of neurological development problems in the babies.

All women in this study, will be offered contraception after giving birth. If you choose not to receive contraception, your treatment will be determined by the local guidelines and the national treatment programme and you will continue with the study follow-up.

### *Potential problem with high sugars*

There have been reports of some people having high sugar levels in their blood after taking dolutegravir. We will measure your sugar levels and take additional samples to look into the reasons why this might happen.

### **Effects relating to the start of treatment**

In some people with advanced HIV infection, signs and symptoms of inflammation from other infections may occur soon after HIV treatment is started. Some people, particularly those that have been HIV positive for a long time, may develop IRIS (mentioned above) which may look and feel like an infection and may be severe. It is thought that these reactions are caused by an improvement in the body's ability to fight infections due to a reduction in the HIV. If you become concerned about any new symptoms or any changes in your health after starting HIV treatment, please discuss with your doctor.

### **What are the possible benefits of taking part?**

Current data suggest that Dolutegravir is able to reduce the HIV viral load more rapidly than other HIV drugs; therefore use in pregnancy may increase the chance of having a low viral load by the time of delivery, which should offer increased protection for your baby. We do not know this for certain, which is why we are doing the study, but by taking part you may have an equal or improved chance of achieving a low HIV viral load by the time you deliver your baby.

### **What if new information becomes available?**

Sometimes during the course of a research project, new information becomes available about the area that is being studied. If you have any questions about it you should discuss this with your study staff member. Any preliminary findings from our research will be communicated with the clinic responsible for your care and communicated through posters and bulletins. Furthermore, any



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new information obtained about the study drug, dolutegravir, will be communicated with the study team and passed on to you.

### **What happens when the research study stops?**

After the study period ends, the study team will make arrangements for you to transfer to the routine care of the ARV clinic. You will continue to take once daily medication (current HIV treatments are to be taken for the rest of your life), but will change from the study combination of medicines to the medicines used throughout the country. If you are still on DTG when you end the study you will have access to DTG post-trial for a period of approximately 6 months after the transition to the NTP.

### **Handling blood and DNA (genetic) Samples**

The samples will be kept in a locked freezer at the Study Site prior to transfer to the University of Liverpool. ALL THESE SAMPLES WILL BE LABELLED WITH A CODE NUMBER ONLY (not your name), but will be linked to details that we will collect about your drug levels or treatment response.

We are asking for your permission to store your samples for these future studies. Your DNA samples will be stored for a period of 5 years or for the period that funding is available for storage. Your samples will be stored safely and securely by the University of Liverpool in the United Kingdom. Only researchers approved by the study team and the University of Liverpool can use the samples for future testing. Your genetic samples will not be sold or used directly to produce commercial products. . (It is not the purpose of this study to produce commercial gain, and in any case, any commercial value in the future will only come from findings in groups of participants rather than from samples from a single participant).

### **Will my taking part in this study be kept confidential?**

Confidentiality will be maintained at all times. All study records and samples will be coded (but it will be possible to link results to data collected without names from this study). Your personal records will be stored separately from your study records. We will combine all the results from this study and present the data on groups of participants (rather than individual participants). No individual will be identifiable from any presentation or publication that ensues from this research.

The University of Liverpool is the sponsor for this study and is responsible for looking after your information and using it properly<sup>1</sup>. Your personal information collected in this research study will be used to improve the health of the public<sup>2</sup>.

Your personal information (coded) including information about your health will be shared with the staff among the study team<sup>3</sup>, who will be responsible to keep your personal information safe and confidential. Also, your coded information may be provided to researchers (outside the study team) running other research studies in this country and abroad. Information that identifies you

<sup>1</sup> The University of Liverpool, UK as the Sponsor for DolPHIN 2 is acting as the Data Controller. The Data Protection Officer, Mrs Victoria Heath, can be contacted on +44 151 794 214.

<sup>2</sup> Legal basis = processing your personal data for DolPHIN 2 is a task in the public interest and done according to UK Policy Framework for Health and Social Care Research.

<sup>3</sup> Study team = researchers from the University of Liverpool (United Kingdom), Liverpool School of Tropical Medicine (United Kingdom), Infectious Diseases Institute (Uganda), University of Cape Town (S. Africa) and Radboud University Nijmegen (The Netherlands).





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will only be seen by authorised people<sup>4</sup> who need to confirm your participation in the study or check the data collection process was done correctly.

Your rights to access, change or move your information are limited, in order to make sure the research remains reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. The data you have provided for DOLPHIN 2 will be stored for 15 years after the study has finished.

If needed your local doctor (see end of this leaflet) can help you find out more or make a complaint<sup>5</sup>.

### **WHAT ABOUT INSURANCE?**

The medication used in this trial is non- experimental and it has been registered in South Africa. The medication has however not yet been registered for use in pregnancy, due to the limited Dolutegravir data on usage in pregnancy. This forms the rationale for conducting this trial. As a participant of the trial you and your infant will be protected in terms of the study staffs' personal malpractice insurance or the university's insurance cover in the event of injury or illness that is caused as a result of participation in this trial.

Compensation will be paid for any injuries to you or your infant attributed to the administration of the study drug, or any procedures adopted to deal with adverse reaction caused directly by the study drug.

#### **'What happens if I get hurt taking part in this study?'**

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 (or latest version), 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,

<sup>4</sup> Authorised people = Sponsor or its delegates and regulators.

<sup>5</sup> You have a right to complaint with the Information Commissioner's Office, United Kingdom by calling +44 303 123 1113.



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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.

It is important to follow the study doctor's instructions and to report straightaway if you have a side effect from the study medicine.

### **What will happen to the results of the research study?**

We will combine all the results from the participants taking part in the study, and publish any results in medical journals. Results presented at scientific meetings may also be viewed at our website <[www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)>. No individuals will be specifically identified in any publication.

A description of this clinical trial will be available at [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) as required by U.S. Law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this website at any time.

We will also ensure that the results of the study are clearly explained to the clinic where you are treated and will produce materials which simply explain the results (for example posters to place on the walls of the clinic).

### **Who is organising and funding the research?**

This study is funded by UNITAID through the University of Liverpool

### **Who has reviewed the study?**

This study has been reviewed by the University of Cape Town Research Ethics Committee. If you want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact Prof Blockman, Chairperson of the University of Cape Town Research Ethics Committee, which is an independent committee established to help protect the rights of research participants at 0214066338.

### **Expenses**

To compensate for inconveniences incurred by this study, you will receive R250 per scheduled study visit for your transport costs.

If you have questions about this trial you should first discuss them with the study doctor or the above-mentioned ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the authority which makes sure that all studies are conducted to the highest possible standards, the Medicines Control Council (MCC) South Africa at:

The Registrar  
Medicines Control Council of South Africa  
Department of Health





**Dolutegravir in Pregnant HIV Mothers and Neonates**

Private Bag X828

PRETORIA 0001

Fax: 012 395 9201 –

Email: [gouwsj@health.gov.za](mailto:gouwsj@health.gov.za)

**Thank you for reading the information about our research project. If you would like to take part, please read and sign this form.**



## Dolutegravir in Pregnant HIV Mothers and Neonates

### PART I

The undersigned, hereafter known as the Study Participant promises the following:

- The information in the volunteer information sheet and the written informed consent form was explained to me.
- All my questions about the study, the possible risks, side effects and taking the study drug have been answered to my satisfaction.
- I agree to take part in the study under the conditions as described in the volunteer information sheet.
- I agree for my partner to be given an abbreviated information leaflet Yes ☐ No ☐
- I agree for samples to be collected from my baby\* Yes ☐ No ☐
- I agree to receive contraception after I give birth\* Yes ☐ No ☐
- I agree to give additional blood samples for sugar measurements Yes ☐ No ☐
- 

*\*will be asked again after delivery*

### PARTICIPANT:

\_\_\_\_\_  
Name of Participant (printed)  
or if illiterate, make a thumbprint \* in the box  
below:

\_\_\_\_\_  
Signature of participant

**Date:** \_\_\_\_ / \_\_\_\_ / \_\_\_\_  
Day Month Year

**Time:** \_\_\_\_ : \_\_\_\_  
Hours Minutes

### PERSON ADMINISTERING CONSENT:

\_\_\_\_\_  
Name of Person Administering Consent (printed)

\_\_\_\_\_  
Position/Title

\_\_\_\_\_  
Signature of Person Administering Consent

**Date:** \_\_\_\_ / \_\_\_\_ / \_\_\_\_  
Day Month Year

**Time:** \_\_\_\_ : \_\_\_\_  
Hours Minutes

*\*If the volunteer is unable to read and/or write, an impartial witness should be present during the informed consent discussion. After the written informed consent form is read and explained to the participant, and after they have orally consented to their participation in the study, and have either signed the consent form or provided their fingerprint, the witness should sign and personally date the consent form. By signing the consent form, the witness agrees that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant and that informed consent was freely given by the participant.*



## Dolutegravir in Pregnant HIV Mothers and Neonates

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**WITNESS:**

\_\_\_\_\_  
Name of Person Witnessing Consent (printed)

**Date:** \_\_\_\_ / \_\_\_\_ / \_\_\_\_  
Day Month Year

\_\_\_\_\_  
Signature of Person Witnessing Consent

**Time:** \_\_\_\_ : \_\_\_\_  
Hours Minutes

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## Dolutegravir in Pregnant HIV Mothers and Neonates

### PART II

#### **Consent for storage and use in possible future research projects.**

I agree that the sample I have given and the information gathered about me can be stored by The University of Liverpool for possible use in future projects as described in the attached information sheet. I understand that some of these projects may be carried out by researchers other than the Liverpool HIV Pharmacology Group who ran the first project.

\_\_\_\_\_ (initial) I agree to have my specimens and data stored for future research by the investigators who are conducting this study or other research collaborators in related areas.

\_\_\_\_\_ (initial) I do not consent to the use of my blood/genital tract sample for any reason outside of this specific study.

### **PARTICIPANT:**

\_\_\_\_\_  
Name of Participant (printed)  
or if illiterate, make a thumbprint \* in the box  
below:

\_\_\_\_\_  
Signature of participant

**Date:** \_\_\_\_ / \_\_\_\_ / \_\_\_\_  
Day Month Year

**Time:** \_\_\_\_ : \_\_\_\_  
Hours Minutes

### **PERSON ADMINISTERING CONSENT:**

\_\_\_\_\_  
Name of Person Administering Consent (printed)

\_\_\_\_\_  
Position/Title

\_\_\_\_\_  
Signature of Person Administering Consent

**Date:** \_\_\_\_ / \_\_\_\_ / \_\_\_\_  
Day Month Year

**Time:** \_\_\_\_ : \_\_\_\_  
Hours Minutes

*\*If the volunteer is unable to read and/or write, an impartial witness should be present during the informed consent discussion. After the written informed consent form is read and explained to the participant, and after they have orally consented to their participation in the study, and have either signed the consent form or provided their fingerprint, the witness should sign and personally date the consent form. By signing the consent form, the witness agrees that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant and that informed consent was freely given by the participant.*



## Dolutegravir in Pregnant HIV Mothers and Neonates

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### WITNESS:

\_\_\_\_\_  
Name of Person Witnessing Consent (printed)

Date: \_\_\_\_ / \_\_\_\_ / \_\_\_\_  
Day Month Year

\_\_\_\_\_  
Signature of Person Witnessing Consent

Time: \_\_\_\_ : \_\_\_\_  
Hours Minutes

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