



Dolutegravir in Pregnant HIV Mothers and Neonates

PARTICIPANT INFORMED CONSENT FORM

D2 -

Chief Investigator: Dr Mohammed Lamorde

Site Locations: Infectious Diseases Institute, Kampala

1 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.

2 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.

3 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 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. Approximately 250 women will be in this study across study sites in Uganda and South Africa.



Dolutegravir in Pregnant HIV Mothers and Neonates

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

5 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 – you will be advised to start treatment now, whether or not you decide to take part in the study. You will be given some time to consider whether you wish to participate in this study. Whilst you need to decide quite quickly because it is important for your health to start treatment the same day, the study team will take great care to ensure that you have made a decision that you are happy with. If you cannot decide, we recommend that you start treatment on the national programme, rather than joining the study. At every study visit, we will make sure you are still happy to remain in the study.

If you agree to take part in the study and we find no reasons for you not to do so following the screening assessment, you will be started on either the standard antiretroviral drugs (containing efavirenz) or the study treatments (containing dolutegravir). This is done by a computer and this means about half the women will be selected to remain on the standard 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 visits at the study clinic approximately seven 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 is 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.

After the first week on your treatment, 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. If a 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 started on dolutegravir, you will need to switch to the medicine that is provided



Dolutegravir in Pregnant HIV Mothers and Neonates

by your local clinics. If the blood results show a medical problem that needs additional care, we will make referrals to doctors who can do this. We would also ask to see you again after two weeks to make sure you are well.

If you remain in the study, we will repeat the ultrasound examination to see how well the baby is growing. We will repeat the ultrasound examination, blood tests and the vaginal sample after four 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 from 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 within two weeks of the birth. We will arrange to see you and your baby in our clinic after six, 12, 24, 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 that is present in your blood and breast milk. We will take a sample from the baby for a HIV at each study visit. 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. As this is the end of the study, we will make arrangements for you to receive ongoing care from the national programme. To make sure there are no interruptions in your treatment, if you have been taking dolutegravir, you will be offered up to six months of dolutegravir whilst you move over to the local ARV clinic.

6 What are side effects/ risks of taking part?

Dolutegravir, the new 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:

Dolutegravir in Pregnant HIV Mothers and Neonates

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"> Headache Feeling sick Loose stools 	<ul style="list-style-type: none"> Rash Itching Vomiting Stomach pain Difficulty in sleeping Dizziness Abnormal dreams Lack of energy Flatulence (gas or wind) Changes in results of blood tests 	<ul style="list-style-type: none"> Allergic reaction Liver problems 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

Most of the side effects listed above have not been very serious, and have not stopped HIV 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 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 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 for 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.



Dolutegravir in Pregnant HIV Mothers and Neonates

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.

Potential problem with weight gain

There have been reports of some people gaining weight after taking Dolutegravir. We will record your weight at each visit and monitor for weight change.

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.

7 What are the possible benefits of taking part?

Current knowledge suggests 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.



Dolutegravir in Pregnant HIV Mothers and Neonates

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

9 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 be given up to 6 months' transitional supply as you move to the National Treatment Programme.

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. Your genetic samples will not be sold for profit.

10 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 properly¹. Your personal information collected in this research study will be used to improve the health of the public².

¹ 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.

² 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.



Dolutegravir in Pregnant HIV Mothers and Neonates

Your personal information (coded) including information about your health will be shared with the staff among the study team³, 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 will only be seen by authorised people⁴ 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 complaint⁵.

11 What happens if I get hurt taking part in this study?

If you become ill or have side effects or injuries because of the study, talk to the study doctor. The study doctor will make sure that you get medical care and advice during the study. The sponsor's insurance will pay for the medical care of illness or injuries caused by the study.

The above statement does not limit your legal rights.

12 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.dolphin2.org No individuals will be specifically identified in any publication.

A description of this clinical trial will be available at 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). Copies of relevant publications will be available via IDI clinic.

13 Who is organising and funding the research?

³ 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).

⁴ Authorised people = Sponsor or its delegates and regulators.

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



Dolutegravir in Pregnant HIV Mothers and Neonates

This study is funded by UNITAID through the University of Liverpool.

14 Who has reviewed the study?

This study has been reviewed and approved by the Joint Clinical Research Centre, Institutional Review Board, an accredited Ugandan Research Ethics Committee (REC) and the University of Liverpool Research Ethics Committee. A REC is a committee that ensures that the rights and welfare of study participants in research are protected. If you want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact Professor Johnson Acon the Chairperson of the JCRC IRB, which is an independent committee established to help protect the rights of research participants at 0414 201 148.

15 Who pays for the study?

You will not be paid for participating in this study. **To compensate for inconveniences incurred by this study, you will receive 30,000 Ugandan shillings per study visit for your transport costs.**

16 Who do I contact for information?

For information about this study you should contact the study doctor or Dr. Mohammed Lamorde at Infectious Diseases Institute, Mulago Hospital Complex, Kampala on tel: 0771-983-618.

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

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. | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| • All my questions about the study, the possible risks, side effects and taking the study drug have been answered to my satisfaction. | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| • I agree to take part in the study under the conditions as described in the volunteer information sheet. | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| • I agree for my partner to be given an abbreviated information leaflet | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| • I agree to provide blood samples | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| • I agree to provide breast milk samples | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| • I agree for vaginal fluid collection | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |

Dolutegravir in Pregnant HIV Mothers and Neonates

- | | | | | |
|---------------------------------------------------------------------------|-----|--------------------------|----|--------------------------|
| • I agree to provide a blood sample and a cord blood sample at delivery | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| • I agree to providing a sample of the placenta | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| • I agree to receive contraception after I give birth* | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| • I agree for blood samples to be taken from my baby* | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| • I agree for throat and stool swabs to be taken from my baby* | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| • I agree to give a blood sample if I am taking contraceptive medication* | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| • I agree to give bloods samples for sugar measurements | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
- *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.*

WITNESS:

Name of Person Witnessing Consent (printed)

Date: ____ / ____ / ____
 Day Month Year



Dolutegravir in Pregnant HIV Mothers and Neonates

Signature of Person Witnessing Consent

Time: ____ : ____
Hours Minutes

PART II - Affirmation of Consent

To be administered after delivery

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

- | | | | | |
|-------------------------------------------------------|-----|--------------------------|----|--------------------------|
| • I agree to provide blood samples | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| • I agree to provide breast milk samples | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| • I agree for blood samples to be taken from my baby | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| • I agree to receive contraception after I give birth | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |

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



Dolutegravir in Pregnant HIV Mothers and Neonates

**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.*

WITNESS:

Name of Person Witnessing Consent (printed)

Date: ____ / ____ / ____
Day Month Year

Signature of Person Witnessing Consent

Time: ____ : ____
Hours Minutes