Bone Loss and Immune Reconstitution in HIV/AIDS (BLIR-HIV)

Informed Consent Form

June 6, 2014

NCT01228318

Emory University and Grady Health System
Consent to be a Research Subject

Title: Bone Loss and Immune Reconstitution in HIV/AIDS

Principal Investigator: Ighovwerha Ofotokun, MD

Sponsor: This study is supported by the National Institute of Health

Introduction
You are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide to consent (agree) to be in the study or not to be in the study. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study.** The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.

Before making your decision:
- Please carefully read this form or have it read to you
- Please listen to the study doctor or study staff explain the study to you
- Please ask questions about anything that is not clear

You can take a copy of this consent form, to keep. Feel free to take your time thinking about whether you would like to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form you will not give up any legal rights.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most the website will include a summary of the results. You may search this website at any time.

Study Overview
You are being asked to volunteer for a research study on how HIV-infection and HIV medicines can affect the human skeleton. Other studies have shown that HIV-infection and HIV medicines (antiretroviral pills or HAART) can cause bone loss. This can lead to osteoporosis --- a condition that makes bone fragile (weak) and fracture easily. This study will look at how HIV virus and HIV medicines affect blood proteins that control bone strength. The study will also examine whether bone loss in this setting can be prevented by giving other medicines that protect the skeleton. This medicine is called Reclast® (zoledronic acid). This medicine is not approved by the Food and Drug Administration (FDA) for use in people with normal bone. However, the FDA has approved the use of this medicine for this study (IND # 108645). If we can understand how to protect the skeleton from the side effect of HIV medicines, we may avoid premature fracture in some patients receiving HAART.

You are being invited to take part because you are HIV-infected and have not received HIV medicines (HAART) in the past, so you might be eligible to take part in this study.

Individuals who volunteer to take part in this study will undergo the following;

- Thorough medical evaluations during study visits
- Begin treatment for HIV-infection with HAART
- Have a 50:50 chance of receive one dose of bone protection medicine or its placebo before starting HAART
- Blood draw for proteins and other measurements
- Total body DXA scan (DXA scan is a special type of X-ray that measures bone density).
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If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any benefits or rights you would normally have if you choose not to volunteer. You can stop at any time during the study. If you stop the study, you will still keep the benefits and rights you had before volunteering. If you decide not to take part in this study, your decision will have no effect on the quality of medical care you receive. If you volunteer to take part in this study, you will be one of 94 people to do so.

Procedures

Where is the study taking place, and how long will the study last?

- Most of the research procedures will be conducted within the Emory University Health Care System and Grady Healthy Care System. The sites will include;
  - The Grady IDP (Ponce Clinic)
  - Grady Memorial Hospital
  - The Radiology Department of the Emory University Hospital.
- DXA-scans will be performed at Emory University Hospital Radiology.
- You will be in the study for about 3 years.

What will I be asked to do?

If you are eligible for this study and do volunteer to take part, you will be asked to do the following:

A. Sign this consent form and the HIPAA Authorization Form.
B. Undergo thorough medical evaluation. This will include
   i. Review of your medical records
   ii. Medical history obtained by study personnel
   iii. Physical examination by study personnel.
C. Have blood collected through your vein after overnight fast.
D. Perform DXA-scans at Emory University Hospital Radiology.
E. Begin HIV treatment with HAART that contain Reyetaz, norvir, and truvada
F. Receive one dose of bone protecting medicine or its saline solution placebo;
   i. Zoledrononic acid (reclast®) giving through your vein
   or
   ii. Placebo (Saline solution) giving through your vein

Study Visits:

The study visits will include

a. Screening visit to determine whether you are eligible
b. Entry visit to register you for the study
c. Thirteen (13) additional **follow-up** visits to monitor your progress during the study.

A. Screening visit:
   - You will be evaluated to see if you are eligible for the study based on the study's criteria

- You will be asked to sign the informed consent and HIPAA forms.
- Your medical record will be reviewed.
- Your HIV-status will be confirmed by reviewing your medical record for previous ELISA, Western blot or HIV-1 RNA PCR (viral load).
- A full medical history and physical will be performed by study personnel
- If you are a woman, urine will be collected for pregnancy test.
- This visit should last for about **one and a half hours** (90 minutes).
- After completing all the procedures listed above, you will be sent to Emory University Hospital Radiology for a DXA-scan.

B. Entry Visit:

1. The entry visit will have 3 separate parts that should be completed within 7 days;

(i) Registration and baseline assessment

- You will be officially registered into the study
- This visit will involve an overnight fast. That means you will be asked not to eat breakfast before coming for this visit.
- 3 tubes (1tablespoon full) of blood will be collected for routine lab tests required as part of standard medical care for your condition.
- Medical history and physical will be performed by study personnel
- 80 ml of blood (about 8 tablespoon full) will be collected for study tests.
- If you are a woman, urine will be collected again for pregnancy test.
- This visit should last for about **one hour** (60 minutes).

(ii) DXA Scan:

- After completing all the procedures listed above, you will be sent to Emory University Hospital Radiology for a DXA-scan.
- This visit should last for about **one hour** (60 minutes).
- This test should occur no later than 7 days after you have been enrolled into the study.

(iii) Randomization (flip of coin)/treatment initiation visit

- The day you complete the DXA scan, you will return to the Ponce to determine which arm of the study you will be assigned.
- You will be randomly assigned to a treatment arm --- just like flipping a coin.
- You will be assigned to begin treatment with one of the following 2 options
  1. HAART (reyetaz/norvir/truvada) + reclast®
  2. HAART (reyetaz/norvir/truvada) + placebo (saline solution)
- An i.v. (intravenous) line will be placed in your vein
- Infusion of either reclast or its placebo will be given to you
- This visit should last for about **one hour** (60 minutes)

C. Follow-up visits (13 in all):

- The 13 visits will occur at weeks 2, 4, 8, 12, 16, 20, 24, 36, 48, 72, 96, 120 and 144 after entry.
- These visits will involve an overnight fast. That means you will be asked not to eat breakfast before coming for these visits.
- Targeted medical history and physical will be performed by study personnel
- If you are a woman of childbearing age, you should let the study staff know if you have any reason to suspect that you may be pregnant during each of the visit.

- 3 tubes (1tablespoon full) of blood will be collected for routine lab tests required as part of standard medical care for your condition at 2, 12, 24, 36, 48, 72, 96, 120, and 144.
- 87 ml of blood (9 tablespoon full) will be collected for study tests at each visit.
- You will fill a brief questionnaire to assess adherence to study medications.
- You will bring your HIV medication bottles for pill counts.
- Each visit should last for about **one hour** (60 minutes).
- At weeks 12, 24, 48, 96, and 144 you will be sent to Emory University Hospital Radiology for follow up DXA-scans.
- If during any of these visits, your lab tests show your HIV is not adequately suppressed, you may be asked to return within 2 weeks for additional blood tests.

Your samples will be stored at the lab. This lab will keep your samples safe and secure for testing during the study. No one will be able to tell that these samples came from you. The samples stored at this lab will not have any data written on them that could identify you. They will not have records stored with them that could identify you. These samples will only be used for research related to this study. Your specimens will only be kept until the study ends. After the study ends they will be destroyed.

If you agree, the researchers may collect an **additional tablespoon (10 cc) of blood sample** for storage during this study. This will occur during the entry visit. Also, if you agree, the research may store leftover samples (blood or body fluid) for additional tests.

These additional samples may be used as a source of DNA for genetic testing that is not yet planned but may be done at a later date. This testing may include studies of HIV, studies of other diseases that affect people with HIV, studies of your cells, proteins, and other chemicals in your body, and studies of your DNA.

If you allow us to do additional tests on your specimens, these specimens will be kept confidential. They will be stored in a building that is secure. They will not be stored together with information that could let someone know that they came from you. Your specimens will be labeled with a unique code; your name will not be written on any specimens.

Risks and Discomforts

I.V. Blood Draw Risk

Blood will be drawn from your veins during the study. The risks associated with vein punctures are uncommon and they include

- Small blood clots in a vein, which can be painful, and
- Infection at the site of needle puncture
- Pain, bruising, soreness, and reaction to tapes at the site of needle insertion
- Some people may experience a fainting spell with needle puncture

These risks occur only on rare occasions.

Low vitamin D and Blood Calcium Levels:

Low blood calcium and vitamin D levels are common particularly among individuals with HIV-infection. Therefore, your blood levels of calcium and vitamin D will be checked at the beginning and regularly during the study. If one or both of them is low, study investigators will recommend that you start taking calcium and/or vitamin D supplements.

Risk of DXA-scan:
This research study involves exposure to radiation from x-rays from DXA procedures. This procedure is routinely used for medical purposes. This radiation dose may not be necessary for your medical care and may occur only as a result of your participation in this study. The radiation dose that you will receive is equal to or less than the natural environmental radiation the average person receives in the United States annually. The principal risk associated with a radiation dose is the possibility of developing a radiation-induced cancer later in life. The risk from radiation exposure of this magnitude is considered to be negligible when compared to everyday risks.

Women who may be pregnant should not participate in this study because of possible effects of radiation exposure on their unborn child. There are currently no studies that show an increase in the risk of genetic mutation in the next generation of offspring.

HIV Medications (Antiretroviral Therapy):
You will be receiving HIV medicines (HAART) as part of routine care for your HIV-infection. Like any other medication, there are side effects associated with HIV medicines. You will be carefully monitored for these side effects by your primary care provider and the study personnel. The risks associated with these medications are listed below.

Immune Reconstitution Inflammatory Syndrome (IRIS): On rare occasion in some people with advanced HIV infection, signs and symptoms of inflammation from other infections may occur soon after anti-HIV treatment is started.

The use of potent anti-HIV drug combinations may be associated with an abnormal placement of body fat and wasting. This is however infrequent. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement

Risks with the Use of Nucleoside Analogues (tenofovir disoproxil fumarate and emtricitabine are nucleoside analogues)

Lactic acidosis (elevated lactic acid levels in the blood) and severe hepatomegaly (enlarged liver) with steatosis (fatty liver) that may result in liver failure, other complications or death have been reported with the use of antiretroviral nucleoside analogues alone or in combination. The liver complications and death have been seen more often in women on these drug regimens. Some nonspecific symptoms that might indicate lactic acidosis include: unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, cramps, muscle pain, weakness, dizziness, and shortness of breath. This side effect is rare.

Tenofovir Disoproxil Fumarate (Tenofovir DF, TDF, VIREAD®)
Gilead Sciences, Inc.

The following side effects have been associated with the use of tenofovir (they are rare to infrequent):

- Upset stomach, vomiting, gas, loose or watery stools
- Generalized weakness
- Dizziness
- Depression
- Headache
- Abdominal pain

- Worsening or new kidney damage or failure
- Inflammation or swelling and possible damage to the pancreas and liver
- Shortness of breath
- Rash
- Muscle pain and muscle weakness
- Allergic reaction: symptoms may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath, a general feeling of illness or potentially serious swelling of the face, lips, and/or tongue
- Bone pain and bone changes such as thinning and softening which may increase the risk of breakage

NOTE: If you are infected with both hepatitis B and HIV, you should be aware that your liver function tests may increase, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen if tenofovir is stopped.

NOTE: Because there is only a small amount of information on tenofovir in pregnant women, tenofovir should be used during pregnancy only if clearly needed.

Emtricitabine (FTC, **Emtriva™***)*
Gilead Sciences, Inc.

The following side effects have been associated with the use of emtricitabine: (they are rare to infrequent):

- Headache
- Dizziness
- Tiredness
- Inability to sleep, unusual dreams
- Loose or watery stools
- Upset stomach (nausea) or vomiting
- Abdominal pain
- Rash, itching, which sometimes can be a sign of an allergic reaction
- Skin darkening of the palms and/or soles
- Increased cough
- Runny nose
- Abnormal liver function tests, which could mean liver damage
- Increases in pancreatic enzyme (substances in the blood), which could mean a problem with the pancreas
- Increased triglycerides
- Increased creatine phosphokinase (CPK), which could mean muscle damage

NOTE: If you are infected with both hepatitis B and HIV, you should be aware that your liver function tests may increase, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen if emtricitabine is stopped.

Emtricitabine, FTC/Tenofovir Disoproxil Fumarate, TDF (TRUVADA™)
Gilead Sciences, Inc.

No new or unexpected side effects are observed with the FTC 200 mg/TDF 300 mg combination tablet than those observed when each drug is given separately.

Risks with the Use of Atazanavir (ATV, Reyataz®)
Bristol-Myers Squibb Company

The following side effects commonly associated with the use of atazanavir given together with ritonavir:
- Increased bilirubin, which may be associated with yellowing of the skin or eyes
- Rash which, may be severe and rarely may cause death
- A change in the way your heart beats (heart rhythm change). Symptoms you may experience if this occurs include dizziness or lightheadedness.
- Worsening of liver disease
- Kidney stones
- Gallbladder disorders such as gallstones and gallbladder inflammation

Other common side effects of atazanavir taken with other anti-HIV medications include:
- Upset stomach
- Headache
- Stomach pain
- Vomiting
- Diarrhea
- Depression
- Fever
- Dizziness
- Trouble sleeping
- Muscle pain

Risks with the Use of Ritonavir (RTV, Novir®)
Abbott Virology

The following side effects are commonly associated with the use of ritonavir:
- Feeling weak and tired
- Stomach and bowel problems, including abdominal pain, upset stomach, vomiting, abnormal stools, and loose or watery stools
- Loss of appetite
- Headache
- Dizziness
- Abnormal increases in triglycerides and cholesterol in blood
- Numbness and tingling in the arms, legs and around the mouth
- Rash
- Abnormal liver function blood tests which may be due to possible liver problems. Liver problems including cases of death have occurred in people taking ritonavir.
- Fever
- A change in the sense of taste
- Pancreatitis (inflammation of the pancreas), which may cause death. If you develop

pancreatitis, you may have one or more of the following: stomach pain, nausea, and vomiting.

- Abnormal heart rhythm and electrocardiogram (EKG) changes. If you develop abnormal heart rhythm you may experience lightheadedness, fainting spells or an abnormal heart beat.

Reclast® (Zoledronic acid):
Reclast is a FDA approved drug for the treatment of osteoporosis (weak bone). Recast on rare occasions may cause serious side effects such as:

- Low vitamin D and Blood Calcium Levels:
  Low blood calcium and vitamin D levels are common particularly among individuals with HIV-infection. The use of reclast may further lower the blood levels of these tests. Symptoms may include numbness or tingling feeling (especially around the mouth) or muscle spasms. Therefore, your blood levels of calcium and vitamin D will be checked at the beginning and regularly during the study. If one or both of them is low, study investigators will recommend that you start taking calcium and/or vitamin D supplements.
- Kidney Problems*:*
  Blood tests to check your kidneys will be performed regularly during the study.
- Jaw-bone Problems (Osteonecrosis of the jaw):
  Jaw-bone problem may occur in some people and include infection, slower healing after teeth are pulled.
- Severe muscle and joint pain:

Below are listed side effects (adverse events) that were reported by 2% or more of patients with osteopenia (thin bone) treated with reclast 5 mg i.v. once per year. These side effects were more common in patients treated with reclast than those treated with placebo (saline solution).

Acute Phase Reaction
The signs and symptoms of acute phase reaction following reclast infusion including,
Fever
Myalgia (muscle aches)
Flu-like symptoms
Headache
Arthralgia
These symptoms occurred within the first 3 days following the dose of reclast and usually resolved within 3 days of onset but resolution could take up to 7-14 days.

Digestive
Nausea (sick at the stomach)
Constipation
Diarrhea
Dyspepsia (heart burn)
Abdominal discomfort

Abdominal distension
Abdominal Pain
Vomiting
Anorexia (loss of appetite)

Vascular Disorder
Hypertension
Atrial fibrillation (irregular heartbeats)

Ear and Labyrinth Disorders
Vertigo (dizziness/spinning around feeling)

Musculoskeletal
Arthralgia (joint pains)
Myalgia (muscle aches)
Pain in jaw
Bone pain

Nervous System Disorders
Headaches
Dizziness
Hypoesthesia (feeling of numbness)

Others
Osteonecrosis of the jaw; the breakdown of the jaw bone (rare)
Renal failure (rare)

New Information
It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

Benefits
Taking part in this study may not help you directly, but it will help us learn more about how HIV and HAART associated bone loss occur and how it can be prevented. This knowledge may help other people in the future. In addition, you may find out about a serious bone condition that you did not know you had.

Compensation
We consider your participation in this study entirely voluntary, and appreciate your time and commitment to research. As compensation for your time, inconvenience, and to assist with the cost of transportation to the Ponce Clinic, you will be paid fifty dollars ($50)for each completed study visit, including the screening, entry and the 13 follow up study visit. If you have to return to the clinic for a repeat procedure from a previous visit, you will receive $25. For those who take public transportation, participants will receive a two-way MARTA Pass for study visits involving a DEXA and a one-way MARTA pass for all other study visits. If you do not finish the study, you will be paid for the visits you have completed. You will not be responsible for the costs of any tests directly related to this study.

Confidentiality
Certain offices and people other than the researchers may look at your medical charts and study records. Government agencies, such as the Food and Drug Administration, and Emory employees overseeing proper study conduct may look at your study records. Study sponsors may also look at your study records. These offices include the Office for Human

Research Protections, the Emory Institutional Review Board, the Emory Office of Research Compliance, the Grady Research Oversight Committee, and the Office for Clinical Research.

There is a Certificate of Confidentiality for this Study:

We will do everything we can to keep others from learning about your participation in the research. To further help protect your privacy, the investigators have obtained a Confidentiality Certificate.

What the Certificate of Confidentiality protects:
The National Institutes of Health has given this study a Certificate of Confidentiality. Emory or Grady Health System would rely on it to not give out study information that identifies you. For example, if Emory or Grady received a subpoena for study records that identify you, we would say no. The Certificate gives Emory or Grady Health System legal backup to say no. It covers information about you that could harm your image or finances. It also covers information about you that could harm your chances at a job or getting insurance.

What the Certificate of Confidentiality does not protect:
The Certificate does not prevent you or someone other than you from disclosing your information. The Certificate does not prevent Emory or Grady from making the following disclosures of information about you:

- Information to state public health offices about certain infectious diseases
- Information to law officials if child abuse has taken place
- Information Emory or Grady gives to prevent immediate harm to you or others
- Information Emory or Grady gives to the study sponsor as part of the research

Research Information Will Go Into the Medical Record:
If you are or have been an Emory or Grady Health System patient, you have an Emory or Grady Health System medical record. If you are not and have never been an Emory or Grady Health System patient, you do not have one. Please note that an Emory or Grady Health System medical record **will** be created if you have any services or procedures done by an Emory or Grady Health System provider or facility for this study. Copies of the consent form and HIPAA patient form that you sign **will** be placed in your Emory Healthcare or Grady Health System medical record.

Emory or Grady Health System may create study information about you that can help Emory Healthcare take care of you. For example, the results of study tests or procedures. These study results **will** be placed in your Emory or Grady Health System medical record. Anyone who has access to your medical record will be able to have access to all the study information placed there. The confidentiality of the study information in your medical record will be protected by laws like the HIPAA Privacy Rule. On the other hand, some state and federal laws and rules may not protect the research information from disclosure.

Emory and Grady Health System do not control results from tests and procedures done at other places, so these results would not be placed in your Emory or Grady Health System medical record. They will not likely be available to Emory or Grady Health System to help take care of you. Emory and Grady Health System also do not have control over any other medical records that you may have with other healthcare providers. Emory and Grady Health System will not send any test or procedure results from the study to these providers. If you decide to be in this study, it is up to you to let them know.

The researchers will review the results of certain study tests and procedures only for the research. The researchers **will not** be looking at the results of these tests and procedures to make decisions about your personal health or treatment. For this study, those things include:

1. DXA Scan reports
2. Blood levels of bone regulating proteins

In Case of Injury

If you get ill or injured from being in the study, Emory or Grady Health System would help you to get medical treatment. Emory, Grady Health System, and the sponsor have not, however, set aside any money to pay you or to pay for this medical treatment. The only exception is if it is proved that your injury or illness is directly caused by the negligence of an Emory, Grady Health System, or sponsor employee. "Negligence" is the failure to follow a standard duty of care. If you become ill or injured from being in this study, your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurer does not pay, then you will have to pay these costs.

If you believe you have become ill or injured from this research, you should contact Dr. Igho Ofotokun at telephone number 404-616-0659. You should also let any health care provider who treats you know that you are in a research study.

Costs

OPTION 1: There are no costs, research or standard of care related, associated with the study.

There will be no costs to you for participating in this study, other than basic expenses like transportation. You will not be charged for any of the research activities.

Withdrawal from the Study

You have the right to leave a study at any time without penalty. If you leave the study before the final planned study visit, the researchers may ask you to have some of the final steps done.

The researchers and sponsor also have the right to stop your participation in this study without your consent if:

- They believe it is in your best interest;
- You were to object to any future changes that may be made in the study plan;
- or for any other reason.

Contact Information

Contact Dr. Ofotokun at (404) 616-0659 or iofotok@emory.edu:

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research

Contact the Emory Institutional Review Board at 404-712-0720 or 877-503-9797 or irb@emory.edu:

- if you have questions about your rights as a research participant.
- if you have questions, concerns or complaints about the research.
- You may also let the IRB know about your experience as a research participant through our Research Participant Survey at http://www.surveymonkey.com/s/6ZDMW75.

If you are a Grady Health System participant, you may also contact Dr. Curtis Lewis, Senior Vice President for Grady Health System Medical Affairs at (404) 616-4261.

Consent

Please, print your name and sign below if you agree to be in this study. By signing this consent form, you will not give up any of your legal rights. We will give you a copy of the signed consent, to keep.

_____

Name of Subject

_____ _____

Signature of Subject Date Time

_____ _____

Signature of Person Conducting Informed Consent Discussion Date Time

_____

Name of Person Conducting Informed Consent Discussion

Attachment 1 of Consent Form

Sample Storage and Future Testing

Please carefully read the statements below and think about your choices. No matter what you decide, it will not affect your care.

If you agree, additional and/or left over samples will be stored and may be used for further tests. Your stored samples will be labeled only with your study number, not your name. Storage of leftover blood is not a requirement to take part in the study and you may take back your approval for the storage of your leftover blood, at any time. If you want your stored samples destroyed during the study or after you have finished the study, you should call the study doctor or nurse and ask that these samples be destroyed. These samples may be held for an indefinite length of time. We cannot ensure that you will be told of the results of the research done on these samples. The information that is obtained from the analysis of your blood samples may be used scientifically. The analysis of your blood samples may contribute to the creation of new diagnostic tests, or other uses that may be commercially valuable. You will receive no financial benefits and may not receive any health-related benefits from such developments.

I agree to have any of my left over samples (blood or other body fluids) stored and used for additional research. This research will be done at a later date and may include genetic testing.

____ Yes ____ No (Please Initial)

I agree to have an additional 1 tablespoon (10cc) of blood taken so that DNA can be collected from it and stored for additional research. This research will be done at a later date, and may include genetic testing.

____ Yes ____ No (Please Initial)