University of Pennsylvania
Research Participant
Informed Consent Form and HIPAA Authorization

Protocol Title:	**A Pilot Study of T cells Genetically Modified by Zinc Finger Nucleases SB-728mR and CD4 Chimeric Antigen Receptor in HIV-Infected Subjects**
Protocol Version	**Version 6; Dated 05-21-2019**
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Why am I being asked to volunteer?

You are being asked to participate in this research study because you are HIV positive and are on stable antiretroviral medication. The doctors at the University of Pennsylvania are studying HIV infection and are attempting to find better ways to treat HIV. Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate your clinical care will not be affected and there will be no loss of benefits to which you are otherwise entitled.

Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. This form also describes the alternative procedures that are available to you and your right to withdraw from the study at any time. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or the research team about this form. If you decide to participate, you will be asked to sign this form. If you decide to participate, you can change your mind at any time and withdraw from the study without giving a reason.

What is the purpose of this research study?

This research study is being carried out to study a new way to possibly treat HIV. As part of this study, we will take some of your own white blood cells, called T-cells, and modify them so that they can identify and target your HIV cells. The modification is a genetic change, or gene transfer, to your normal T-cells. These modified cells are called CD4 CAR+CCR5 ZFN modified T cells.

The use of CD4 CAR+CCR5 ZFN modified T cells is experimental and has not been approved by the US Food and Drug Administration (FDA). While modified T-cells using each of these modifications have been evaluated in participants as part of other research studies, this is the first time cells using all of these modifications at the same time are being evaluated in participants. These T cells will be given back to you through a single infusion.

The purpose of this research study is to evaluate the safety of the CD4 CAR+CCR5 ZFN modified T cells and determine whether they have any effect on HIV infection.

All participants in this study will receive **CD4 CAR+CCR5 ZFN** modified T cells at the same dose level, followed by a planned treatment interruption where you stop taking your routine antiretroviral medication. The purpose of this planned treatment interruption is to let the antiviral drugs wash out of your body, so that the effects of the immune system and the **CD4 CAR+CCR5 ZFN** T cells on the HIV infection can be measured.

Participants in this study will be broken down into two groups (or cohorts). You will be randomized (assigned by chance, like by the flip of a coin) to either Group 1 or Group 2. In Group 1, participants will begin this treatment interruption approximately 24 hours after they receive the modified T-cells. In Group 2, participants will begin this treatment interruption approximately 8 weeks after they receive the modified T-cells. Your study doctor will explain which group you have been assigned to as part of your participation.

An overview of the study is provided in the table below.

<table>
<tr><th></th><th>STEP 1</th><th>STEP 2</th><th>STEP 3</th><th>STEP 4</th><th>STEP 5</th><th>STEP 6</th></tr>
<tr><td>GROUP 1</td><td rowspan="2">Apheresis and Cell Manufacturing</td><td rowspan="2">Receive CD4 CAR+CCR5 ZFN Modified T Cells on Day 0</td><td><u>Group 1</u>
Stop HIV Medication 24 Hours After You Receive the Modified T Cells</td><td rowspan="2">OPTIONAL:
Stop Taking HIV Medication for an Additional Period as Long as Your Viral Load Remains Low</td><td rowspan="2">Restart HIV Medication and Remain on It Until Your Viral Load Returns to a Low Amount</td><td rowspan="2">Secondary Follow-up for Up to 5 Years</td></tr>
<tr><td>GROUP 2</td><td><u>Group 2</u>
Stop HIV Medication 8 Weeks After You Receive the Modified T Cells</td></tr>
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How long will I be in the study? How many other people will be in the study?

It is expected that 12 participants will receive CD4 CAR+CCR5 ZFN modified T cells as part of this research study at the Hospital of the University of Pennsylvania. Your participation in this study will last up to 5 years from your T-cell infusion. After you complete participation in this study, you will be asked to participate in a separate long-term follow-up study where your health will continue to be monitored for another 10 years (for a total of 15 years of follow-up after your T-cell infusion).

What am I being asked to do?

Prior to taking part in this study, you and your doctor should discuss the current standard treatments for HIV, including all alternative medical options. The study doctor will ask you to read and sign this Informed Consent Form after all of your questions have been answered. At any time during the study, you will have the opportunity to ask questions and receive responses in terms that are understandable to you.

Once you decide to participate, you will have to undergo a process to determine if you are eligible to participate in this study. This process is called screening.

Step 1: Screening/Enrollment and Baseline Procedures

Step 1 of this study includes baseline evaluations to determine your eligibility to participate, and collection of your white blood cells to manufacture the CD4 CAR+CCR5 ZFN modified T cells.

Group 1 & 2	***STEP 1: Manufacturing (Prior to Your T Cell Infusion)***			
Study Time Point	**Screening**	**Apheresis**	**Apheresis #2** Week -4 to -3	**Safety Evaluation Visit** Within 14 days of T cell infusion

<u>Prior to your T-cell Infusion</u>.
In order to determine if you are eligible to participate in this study, you will undergo the following tests/procedures:

1) *Physical examination* – examination and assessment of your vital signs (including temperature, blood pressure, and heart rate)
2) *Detailed medical history* – the doctor or study nurse will ask you about all previous medical conditions, current medications, participation in any prior clinical trials, and documented CD4+ nadir, and historic viral load set point. Your

set point is the point, or level, at which your viral load has stabilized after the initial high viremia associated with early HIV infection.

3) *Blood Tests* (approximately 3 tablespoons) – to make sure you are healthy enough to participate. This will include:
    - Routine Blood Tests - to assess your blood cell counts, blood chemistry levels (to test your organ function and the minerals in your blood), CD4 count, and viral load;
    - Pregnancy Test - to see if you are pregnant (for females of childbearing potential);
    - Hepatitis Testing - a disease that affects how your liver functions);
        i. Reporting of a positive Hepatitis B and/or Hepatitis C test: You will be tested for Hepatitis B and Hepatitis C as one of the screening requirements prior to participating in this study. If you test positive for Hepatitis B and/or Hepatitis C, by law we have to report the positive test results to the City of Philadelphia Health Department and/or the PA Department of Health. Personal identifiers such as name, sex, date of birth, address, and phone number will be reported. For more information about the requirements reporting infectious diseases to the City of Philadelphia Health Department, please visit https://hip.phila.gov/ReportDisease. For more information about the requirements reporting infectious diseases to the PA Health Department, please visit http://www.health.pa.gov/Your-Department-of-Health/Offices%20and%20Bureaus/epidemiology/Pages/Reportable-Diseases.aspx#.V620aZ3D9eU
    - CCR5 Genotyping
    - Blood for research testing
4) *Examination of your veins* - a nurse or doctor will look at the veins in your arms to make sure you have good enough veins to undergo a procedure (called apheresis) that will be used to collect your T-cells.
5) *An electrocardiogram* (or "EKG") - a test to check for problems with the electrical activity/rhythm of your heart.
6) *Urine Sample* - to check for infection

Once you have completed the screening visit, your study doctor will determine whether you are eligible to continue your participation in the study.

Apheresis Visit #1- Prior to your T-cell Infusion.
Once the above screening procedures have been completed and your study doctor determines you are eligible to participate in this study, you will be scheduled for your first apheresis procedure.

Apheresis is a procedure in which a portion of your white blood cells are removed from your blood. You will have one needle inserted in each arm. The machine will take blood from the vein in one arm through tubing and passes through a machine called an apheresis machine which will separate your T-cells from the rest of your blood and then return the blood not collected through the tubing and back to you in your other arm. This is a sterile procedure and uses a solution called Acid-citrate-dextrose (ACD) and a salt solution (called saline) during the process to prevent your blood from clotting within the tubing of the machine. A small amount of this solution will also be returned to you along with your red blood cells and platelets during the process. This procedure usually lasts around two to three hours. The apheresis procedure is necessary in order to collect your white blood cells to make the CD4 CAR+CCR5 ZFN modified T cells. Mini-apheresis procedure collects fewer white blood cells and last ~1 hour.

This procedure will take place in an apheresis unit at the Hospital of the University of Pennsylvania. This apheresis visit will take ~4 hours in total and the apheresis procedure will take ~ 3 hours to complete. Your cells collected as part of this apheresis procedure will be used to manufacture the CD4 CAR+CCR5 ZFN modified T cells you will receive as part of this study. It will take about 3-4 weeks for these T-cells to be manufactured in the laboratory.

Second Apheresis - Approximately Week -4 to -3 Prior to your T-cell Infusion.
If your CD4 CAR+CCR5 ZFN modified T cells are successfully manufactured from the first apheresis procedure, the second apheresis will collect fewer cells and last ~ 1 hour (mini-apheresis). However, if the first apheresis procedure is not successful, the duration of the second apheresis will be similar to the first apheresis procedure in that the visit will take ~ 4 hours in total and the apheresis procedure will take ~ 3 hours to complete.

If the first and second apheresis procedures are not successful, you will be removed from the study.

Safety Evaluation Visit- Within 14 days (+/- 3 days) of your T-cell infusion
Prior to receiving the study treatment, you will return to the clinic to make sure you are healthy enough to receive your CD4 CAR+CCR5 ZFN modified T cells. Assessments performed at this visit include a physical examination, assessment of your vital signs, routine blood tests, pregnancy test (if you are a female of childbearing potential), and collection of a urine sample. About 2 tablespoons of blood will also be collected for research analysis.

At this visit, your study doctor will also discuss the plan for you to stop taking your antiretroviral medications which will occur after your T cell infusion. The timing of when this treatment option will occur depends on which Study Group you have been assigned to. In Group 1, participants will begin this treatment interruption approximately 24 hours after they receive the modified T-cells. In Group 2, participants will begin this treatment interruption approximately 8 weeks after they receive the modified T-cells. There are several approaches to begin the treatment interruption. Your doctor will discuss the options with you given your particular antiviral medications, and you will choose which approach to use for stopping the antiviral medications.

Step 2: T-cell Administration and Safety Follow-up

Administration of CD4 CAR+CCR5 ZFN modified T cells

On the day of your CD4 CAR+CCR5 ZFN modified T cells you will undergo tests/procedures including a targeted physical examination, routine blood tests, urine pregnancy test (if you are a female of childbearing potential), and collection of a urine sample. Blood samples for research purposes will also be drawn before your infusion and at 20 minutes and 2 hours after your infusion (approximately 5 tablespoons).

In order to administer the CD4 CAR+CCR5 ZFN modified T cells, a nurse will place an IV into your vein using a needle. You will then receive premedications to prevent potential side effects of T-cell treatment, including acetaminophen (e.g., Tylenol) and/or diphenhydramine (e.g., Benadryl). Diphenhydramine may make you feel drowsy and so you should be cautious about driving immediately afterwards if you feel tired.

The T-cells will take less than 20 minutes to go into your vein. Your vital signs (temperature, blood pressure, heart rate, respiratory rate and blood oxygen levels) will be monitored before your infusion, and for up to 2 hours after your infusion to ensure they are satisfactory and stable. If your vital signs are stable and you do not experience any uncomfortable effects from the infusion, you will be able to leave the hospital. You will be asked to return to the clinic the next day in order to monitor your health and for follow-up testing. It is possible that you may experience side effects that will require you to be admitted into the hospital until you are stable.

Safety Follow-up Visit- 24 hours after your T cell Infusion

All participants will be asked to return to the clinic the day after their T cell infusion for a safety follow-up visit. Assessments performed at this visit include a targeted physical examination, assessment of any side effects you may be experiencing, routine blood tests, EKG, and collection of a urine sample. About 2 tablespoons of blood will also be collected for research analysis.

Participants enrolled in Group 1, will move onto Step 3 (Treatment Interruption) beginning 1 day after their T Cell infusion (after completion of the 24 hour study visit). Participants enrolled in Group 2, will remain in Step 2 follow-up for 8 weeks after their T cell infusion, and will move onto Step 3 (Treatment Interruption) after the Week 8 post-infusion study visit. These differences are highlighted in the Tables below.

Group 1	***STEP 2: Administration of CD4 CAR+CCR5 ZFN modified T cells + Anti-Retroviral Therapy (ART)***		***STEP 3: Treatment Interruption***									
Study Time Point	**Day 0**	**24 hrs**	**48 hrs**	**Week 1 ± 3d**	**Week 2 ± 3d**	**Week 4 ± 7d**	**Week 6 ± 7d**	**Week 8 ±7d**	**Week 10 ±7d**	**Week 12 ±7d**	**Week 14 ±7d**	**Week 16 ±7d**

d = days

Group 2	***STEP 2: Administration of CD4 CAR+CCR5 ZFN modified T cells + Anti-Retroviral Therapy (ART)***								***STEP 3: Treatment Interruption***								
Study Time Point	**Day 0**	**24 hrs**	**48 hrs**	**Week 1 ± 3d**	**Week 2 ± 3d**	**Week 4 ± 3d**	**Week 6 ±3d**	**Week 8 ±3d**	**Week 1 ±3d**	**Week 2 ±3d**	**Week 4 ±3d**	**Week 6 ±7d**	**Week 8 ±7d**	**Week 10 ±7d**	**Week 12 ±7d**	**Week 14 ±7d**	**Week 16 ±7d**

d = days

Group 2 Participants - Additional Step 2 Safety Follow-up Visits

Participants in Group 2 will be asked to return to the clinic for additional Step 2 Safety Follow-up Visits at the following time points. Assessments performed at these visits include physical examinations, assessment of any side effects you may be experiencing, routine blood tests, and collection of a urine sample. About 2 tablespoons of blood will also be collected for research analysis at each visit.

- 48h post-infusion.
- Day 7 ± 3 post-infusion
- Day 14 ±3 post-infusion
- Day 28 ±7 post-infusion
- Day 42 (Week 6) ±7 post-infusion

- Day 56 (Week 8) ±7 post-infusion- at this visit you will also be asked to undergo another apheresis procedure.

Step 3: Treatment Interruption

Group 1:
Participants enrolled in Group 1, will move on to Step 3 (Treatment Interruption) beginning 1 day after their T Cell infusion (after completion of the 24 hour study visit). During Step 3, participants will begin a treatment interruption from their antiretroviral medications. During Step 3, you will be asked to return to the clinic every 1-2 weeks for about 16 weeks. Assessments performed at these visits include physical examinations, assessment of any side effects you may be experiencing, routine blood tests (including CD4 count and viral load), and collection of a urine sample. About 2 tablespoons of blood will also be collected for research analysis at each visit.

Group 2:
Participants enrolled in Group 2, will remain in Step 2 follow-up for up to 8 weeks after their T cell infusion, and will move onto Step 3 (Treatment Interruption) after completion of the Week 8 post-infusion study visit. During Step 3, participants will begin a treatment interruption from their antiretroviral medications. During Step 3, you will be asked to return to the clinic every 1-2 weeks for about 16 weeks. Assessments performed at these visits include physical examinations, assessment of any side effects you may be experiencing, routine blood tests (including CD4 count and viral load), and collection of a urine sample. About 2 tablespoons of blood will also be collected for research analysis at each visit.

Both Groups:
During the treatment interruption step, your blood may be tested for antiretroviral medication levels. This is to monitor adherence to the treatment interruption in order to be sure that the data collected is true to the study design, and not impacted by anti-HIV medications.

If during the treatment interruption, the physician or study doctor finds that your HIV is at or above 100,000 copies per ml repeatedly over a period of 3 weeks or your CD4 cell counts drops to either a) 350 or below, or b) 50% or less of the baseline CD4 count and remains so after a second reading 1-3 days later, your study doctors will recommend that you stop treatment interruption and immediately restart your HIV medications. The type of medication you receive will be determined by your doctor. It is likely that you will resume the same medications you were taking before the planned treatment interruption. If your viral load is under control (at or under 1000 copies per ml) at the end of your planned treatment interruption, and you decide not to restart your HIV medications at that time, you will enter Step 4 of the study and be followed every 2 weeks. When you restart your HIV medication, you will move directly to Step 5 of the study. Please see below for additional details.

Additionally, if you develop Acute Retroviral Syndrome, a syndrome in which the HIV virus is duplicating at a rapid rate and causing flu-like illness, with symptoms that persist for more than 1 week or affect your normal activities of daily living for more than 1 week, HIV medications will be restarted.

Prior to restarting your HIV medication, you will also be asked to undergo another apheresis procedure (to measure the amount of any remaining immune cells that are infected with inactive HIV virus and to detect for the presence of CAR T cells you received).

Step 4: Treatment Interruption Extension

If your viral load is under control (at or under 1000 copies per ml) at the end of your planned treatment interruption, and you, your study doctor, and your personal physician decide not to restart your HIV medications at this time, you will enter Step 4 of the study (Treatment Interruption Extension) and will be followed every 2 weeks. You will remain in Treatment Interruption Extension as long as your viral load is under control (at or under 1000 copies per ml) or until you decide you want to restart your HIV medications even if your viral load is under control.

Assessments performed at these visits include physical examinations, assessment of any side effects you may be experiencing, routine blood tests (including CD4 count and viral load), and collection of a urine sample. About 2 tablespoons of blood will also be collected for research analysis at each visit.

When you restart your HIV medication, you will move directly to Step 5 of the study and be tested for drug resistance to make sure you are taking medication that will be effective against your HIV.

Step 5: Re-initiation of HIV Medication

Step 5 of the study begins once you re-start your HIV therapy. During Step 5 you will be followed monthly until your viral load has fallen below the level of detection. This may take less than six months. Assessments performed at these visits include physical examinations, assessment of any side effects you may be experiencing, routine blood tests (including CD4 count and viral load), and collection of a urine sample. About 2 tablespoons of blood will also be collected for research analysis at each visit.

Once your viral load has fallen below the level of detection, you will enter Step 6 of the study (Secondary Follow-up). Prior to entering Step 6 of the study you will be asked to undergo a final apheresis procedure.

Step 6: Secondary Follow-up

Once you complete primary follow-up as outlined above, you will enter into Step 6 (Secondary Follow-up) for up to 5 years after your T cell infusion. During Secondary Follow-up you will be asked to return for follow-up visits every 3-6 months. Your first visit in Secondary Follow-up will be based on when you discontinue Primary Follow-up (above) and the amount of time that has passed since your T cell infusion.

Assessments performed at these visits include physical examinations, assessment of any side effects you may be experiencing, routine blood tests (including CD4 count and viral load), and collection of a urine sample. About 2 tablespoons of blood will also be collected for research analysis at each visit.

Additional Blood Collection:
In the event something unexpected occurs to you during your participation in the protocol, the research team may request an additional blood draw be performed to collect additional blood samples for research analysis. This is being done with the intention of evaluating the likely effects from the investigational product you have received. The total amount of extra blood that will be collected from you will be 3 tablespoons of blood twice in one week, in addition to the protocol-specified time points. The potential risks from drawing this extra blood is unchanged from the risks listed below in “risks associated with blood draws”.

In addition, if during your participation in this study you undergo additional blood collection as part of your routine care (such as CD4 counts and viral loads), the results of these tests may also be used for research purposes.

The study team may “bank” (store) some of your blood samples collected throughout your participation in this study. These samples will be kept frozen and will not identify you by name. The blood samples will only be used by the study team to go back and do testing on your blood if an unexpected event occurs.

Long-Term Follow-Up Study

After you complete this research study, you will be asked to enroll in a separate long-term follow-up research study that will look for possible side effects of the gene modified T cells. If you choose to participate in the long-term follow-up research study, you will sign a new separate consent form. The long-term follow-up research study will consist of annual evaluations for up to 10 more years.

Request for Autopsy
In order for the study doctors to learn more about your HIV status and the effects of the CD4 CAR+CCR5 ZFN modified T cells, we may request to perform an autopsy in the unlikely event your death is suspected to be related to the modified T cells you received. Your family will make the final decision as to whether or not an autopsy can be performed and will be asked to sign forms that will authorize the autopsy. Therefore,

please inform your family of your wishes. If an autopsy is performed, samples obtained during this procedure will be used for research purposes. The purpose of this request and results from your study participation will not be revealed to your family. Your HIV status will remain private. The only information shared with your family will be your cause of death.

What are the possible risks or discomforts?

Risks associated with highly active antiretroviral therapy (HAART) treatment interruption:
Analytical treatment interruptions are defined breaks from taking anti-retroviral HIV medications. These interruptions are accepted tools in the evaluation of immunological interventions or therapeutic vaccines for the treatment of HIV infection. Analytical treatment interruptions are for research purposes, and are not a part of the standard care regimen for treating HIV. In order to minimize the risk associated with treatment interruptions, the duration of these interruptions is designed for 16 weeks. This duration allows the participant to reach a new viral load "set point", which is defined by the AIDS Clinical Trial Group as the average of week 12 and week 16 post treatment interruption values. By extending the analytical treatment interruption (ATI) to 16 weeks and allowing the viral load to increase to as much as 100,000 copies/mL for up to 3 weeks, we believe we can better define the new set point. These parameters will allow for any enrichment and expansion of the modified cells to occur, and correspondingly allow for observation of the effects these modified cells have on viral load, while still not compromising study participant safety.

Possible side effects from stopping antiretroviral therapy include the development of drug resistant HIV, lower CD4 T cell counts, and higher viral loads, which could cause a worsening of your HIV infection. Patients with low CD4 nadir who undergo treatment interruption may be at increased risk due to poorer CD4 recovery. To minimize this risk, you must have a CD4 nadir of no lower than 200 cells/mm^3 before you enter this study.

The size of the latent HIV reservoir could also potentially increase, with uncertain clinical consequences. The latent HIV reservoir is a group of immune cells in the body that are infected with HIV but are not actively producing new HIV. Additionally, although not expected from a short term treatment interruption, there is a possibility that death could indirectly result due to disease progression and severe complications of HIV. There is also the risk of other clinical events not related to HIV.

Possible restriction from other clinical research requiring a set period of undetectable viral load may occur, until that time period has passed after restart of HIV medication and achievement of undetectable viral load (VL).

It is possible you could develop Acute Retroviral Syndrome, during which the HIV virus is duplicating at a rapid rate. This syndrome is characterized by flu-like symptoms

including fever, sore throat, diarrhea, joint or other body aches, rash, headache, fatigue, and swollen lymph nodes.

During treatment interruption it is likely you will have a detectable viral load, which increases the risk of transmission to sexual partners. Precaution should be taken with all sexual partners, and barrier methods of protection (condoms) should be used to minimize this risk.

The U.S. Department of Health and Human Services (DHHS) recommendation is for all HIV-infected individuals to be on antiretroviral therapy (ART), with the goal of sustained viral load suppression; ART should be continued indefinitely.

The clinical trial you are participating in will allow you to remain off of your drugs until your CD4 count falls to 350 or below. Due to the DHHS Guidance, this CD4 count is no longer the standard of care for HIV treatment. Since the duration of the treatment interruption is 6 months or less, we believe this treatment interruption is still safe for you to do. You may want to discuss this DHHS Guidance with your primary HIV doctor, or discuss any questions you may have with Dr. Tebas or the study nurse.

Cytokine Release Syndrome/Macrophage Activation Syndrome:
Rapidly growing activated CAR T cells may release proteins and chemicals called cytokines. Release of large amounts of certain cytokines can cause a “cytokine release syndrome”. Macrophage activation syndrome is an activation of your immune system associated with the cytokine release syndrome. The majority of what is known about cytokine release syndrome and macrophage activation syndrome has been learned from cancer patients treated with CAR T cells. Cytokine release syndrome can cause a severe flu-like syndrome. Symptoms of this severe flu-like syndrome include high fevers, chills and shaking, muscle aches, joint aches, sweating, nausea, vomiting, loss of appetite, fatigue, headache, fast heart rate, liver problems, and kidney problems requiring dialysis. People can also have trouble breathing and dangerously low blood pressure. Some people need to be treated with a ventilator (a breathing machine). Many people with severe flu-like syndromes have had to be cared for in an intensive care unit at the hospital. This reaction can be mild or severe and has resulted in death.

These side effects may or may not be reversible. Medications are available to potentially reverse the cytokine release syndrome and macrophage activation syndrome (steroid treatment or other medicines). Unfortunately, some these medicines could get rid of the CAR T cells and prevent them from working. The best time to administer medications to treat the cytokine release syndrome and macrophage activation syndrome is not currently known. In addition, these medications may weaken the immune system increasing the chance for potential serious infections (including but not limited to pneumonia).

In addition, some participants have become very confused and disoriented (unaware of who they are and or where they are, not recognizing family and friends, unaware of the

date and unaware of their health problems). Some participants have had seizures or have even become unresponsive. We believe these side effects are caused by the cytokine release syndrome and macrophage activation syndrome. In some instances these problems resolved when we treated the participants with medications that reverse the cytokine release syndrome.

Significant decreases in blood counts, including neutropenia (low white blood cell count), anemia (low red blood cell count), and thrombocytopenia (low platelet counts) are routinely seen in cancer patients treated with CAR T cells. This may be related to the chemotherapy that may have been received prior to the CAR T cell infusion, and may be related to the CAR T cell infusion as well. These decreases can last weeks or, much more rarely, months. These decreases may result in the need for transfusions (i.e. anemia and thrombocytopenia) and increase the risk of severe infections. It is unknown whether similar reactions to those experienced by cancer patients will be seen in HIV patients.

Vaccine administration during the trial:
Routine vaccines are prohibited prior to completion of Step 5 unless medically indicated.

It is also recommended that enrolled participants should not receive their influenza vaccine during the treatment interruption as it may cause a transient increase in viral load in some participants. If medically indicated while on study, every attempt should be made to receive the influenza vaccine prior to Step 2 or after entry into Step 5.

There may also be unknown risks associated with this clinical trial because this is the first time the CD4 CAR+CCR5 ZFN modified T cells are being tested in humans. Below are listed the risks that the investigators think are possible with this study.

The following side effects may be observed with CD4 CAR+CCR5 ZFN modified T cells:

- Chills and fever
- Headache, myalgia, arthralgia
- Increase in blood pressure
- Low heart rate
- Allergic reaction (itching, swelling of the tongue)
- Seizures
- Nausea and vomiting
- Injection site reactions such as bruising, swelling, black and blue marks, fainting and/or infection at the site
- A decrease in hemoglobin and hematocrit (red blood cell number, called anemia)
- Worsening of your HIV infection (increase in HIV-1 viral load or decrease in T cell count)
- You may be excluded from future gene therapy or vaccine trials as a result of your participation in this study.

Potential risks of falsely elevated viral load results:
The study vector used to manufacture the CD4 CAR+CCR5 ZFN modified T cells can cause a falsely elevated viral load result depending on the viral load test used. During your study participation, a specific viral load test (Hologics) that does not detect the study vector will be used. During the study we will be
obtaining the viral load results using this method. In the future, you or your doctor may need to request this version of the test if the CD4 CAR+CCR5 ZFN modified T cells remain detectable in your blood.

Risks associated with antibody formation:
Your white blood cells isolated by the apheresis procedure will have further processing that will isolate and expand the T-cells needed for your treatment. The separation is accomplished by using a system in which mouse antibodies are used. Residual mouse antibodies, which are proteins that are foreign to your body, can elicit an antibody response in your body. Furthermore, it is also possible that you may develop antibodies to other residual proteins that may not have been completely removed during the manufacturing process. The result of this is that your body could develop antibodies to the "foreign" proteins which could lead to an allergic reaction, such as skin rash, itching and fever. More serious allergic reactions that require medical treatment could also occur, such as shortness of breath and drop in your blood pressure. Rigorous tests are in place to make sure that foreign residual proteins are completely removed, but it is possible that some residual protein could remain.

Potential Risk of Blood Cancer:
This study involves giving you your own cells whose DNA has been changed with a delivery vehicle for the study drug you are receiving. The study drug makes a permanent change in the DNA of the cells you are receiving. There is a risk that genetic changes to your cells may make the cells turn into cancer. This risk is primarily associated with a class of viral vectors (called retroviral vectors) used to deliver genes into cells.

Potential risk of other cancers:
There is a chance that the genetic modification made to your T cells could cause other cancers. This could be caused by the virus (called a vector) used to genetically modify your T cells. In a prior gene therapy study for a childhood disease called Severe Combined Immunodeficiency (SCID), a viral vector caused leukemia in a small portion of patients. Some that developed the leukemia were successfully treated while others were not. The vector used in the SCID study is different than the vector used in this research study.

Other cancers have been observed in patients who have received CAR Therapy. The relationship of these cancers to the CAR therapy is not known at this time. Based on the way the vector used in this study works, we think the risk of the vector causing other cancers is low.

While this risk is low, you will be monitored for development of any new cancers throughout the scheduled protocol visits. If a new cancer develops while you are on study, you will be treated by standard of care clinical procedures, and the cancer will be investigated to determine if the lentiviral vector contributed to its development.

Reproductive risks:
The effects of CD4 CAR+CCR5 ZFN modified T cells on pregnancy and child development are unknown. Therefore, there could be serious harm to unborn children (or children who are breast-feeding) and it could also jeopardize the health of the mother.

Additionally, during the treatment interruption step, viral load is anticipated to reach detectable levels, and therefore could be transmitted to sexual partners or passed on to infants during childbirth or breastfeeding. Pregnancy and breastfeeding should be avoided.

If you are currently pregnant, it is important that you inform the investigator because you will not be able to participate in the study. If you are able to become pregnant, you will be given a serum pregnancy test before entry into the study. You should not become pregnant while you are taking this drug and for 12 months from your T cell infusion. If you do become pregnant, you must tell the investigator and consult an obstetrician or maternal-fetal specialist.

To ensure participant safety, each pregnancy in a participant on study treatment must be reported to the sponsor within 24 hours of learning of its occurrence. The pregnancy will be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancies will also be reported to the Antiretroviral Pregnancy Registry.

If you are a male participant and your partner becomes pregnant, you must tell the study doctor as soon as possible. Pregnancy and outcomes monitoring for safety will be performed as is done for a female participant who becomes pregnant.

Male and female participants are asked to use two medically accepted methods of birth control with their partners for the duration of the study such as condoms, diaphragm or cervical cap with spermicide, intrauterine device, and hormonal contraception. Condoms are recommended because they are the only birth control method that functions as a barrier for HIV infection while you participate in the study.

Risks associated with apheresis*:*
Side effects that can occur during the apheresis procedure include nausea, vomiting, fainting or dizziness, seizures, skin rash, hives, flushing (redness and warmness of the skin, usually the face), blood loss, and infection. Tingling of the lips, muscle cramping and, very rarely, changes in the heart rhythm can occur. These can be prevented or

made milder by giving calcium supplements, either by mouth or in the vein, also called intravenous (IV). Very rarely, (less than 1 in 1,000 procedures), clotting may occur in the apheresis machine or in a patient and is potentially life-threatening. To reduce the risk of clotting, you will be given a drug called ACD (acid-citrate-dextrose). This drug may increase the risk of bleeding and may cause temporary tingling of the lips and limbs, muscle cramping, seizures, or changes in the heart rhythm. After the apheresis procedure you may experience temporary discomfort, including irritation, swelling or bruising at the place where the needle was inserted into your vein to collect the blood. Apheresis can also occasionally cause: hives, numbness and tingling, or swelling of your feet and ankles.

Risks associated with blood draws:
Occasionally there are risks associated with blood draws such as bruising, swelling, black and blue marks, fainting and/or infection at the site. You may also experience a decrease in red blood cell number (called anemia) from having blood drawn frequently. During your participation in this study, which may last for up to 1 year, approximately 31 ¾ - 38 ½ tablespoons of blood (about 2-2 ½ cups) will be drawn for research purposes. The amount of research blood during Secondary Follow-up which will last up to 5 years will be approximately 16 ¼ tablespoons (about 1 cup).

Risks of Genetic Testing:
Additional research performed using your blood samples may include genetic testing. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

There can be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Even though your genes are unique, you share some of the same genes with your blood relatives. Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because your samples will be coded. Research results will not be returned to you or your doctor.

Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, it could make it harder for you to get or keep a job or insurance, or life insurance companies may charge a higher rate based on this information. We believe the chance these things will happen is very small, but we cannot make guarantees.

A federal law (Genetic Information Non-Discrimination Act, GINA) helps reduce the risk from health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long term care insurance. If you want to learn more about GINA, you can find information about it on the internet or ask the study staff.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

You should not expect to receive any benefit from this study. This study is primarily designed to test safety.

What other choices do I have if I do not participate?

The alternative is to not participate in the research and to consider other anti-HIV treatment that your doctor has suggested. You do not have to participate in this study to receive treatment for your HIV illness. If you decide not to participate in this study you will continue to be treated by your primary physician.

Will I be paid for being in this study?

You will receive up to $3000 for completing this study to compensate you for your time and effort. Compensation will be paid via ClinCard (a secure, reloadable debit card). The payment will be $50 per study visit, with the following exceptions:

STEP 1
Completion of Apheresis 1 and visit.....$150
Completion of Apheresis 2 and visit.....$150

STEP 2
Completion of Infusion $75
Completion of Apheresis.....$150

STEP 3
Completion of Apheresis.....$150

STEP 5
Completion of Apheresis.....$150

Estimated total compensation for the trial **$2275-3000**

Please note: In order to be compensated for your participation in this study, you will be asked to provide your Social Security Number. Additionally, please note that the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year because this income is taxable to you.

Will I have to pay for anything?

The research study will cover the cost of research related tests, procedures and clinic visits. There is also no cost for the investigational T-cell product and apheresis procedure that you will receive during your participation.

This research study also requires that you receive certain standard medical tests and examinations during the course of the research study. These exams, tests or procedures are part of routine care and may be done even if you were not in this research study. The costs of these standard tests and examinations will be the responsibility of you and/or your health insurance provider. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this research study may or may not cost your insurance company more than the costs of getting regular treatment for your HIV. You are expected to pay for any costs not paid by your insurance provider (including co-pays and deductibles).

You and/or your health insurance will also be billed for the costs of medical care during this study if the medical care is not included in or related to this study.

Will I receive the results of research testing?

Most tests done in research studies are only for research and have no clear meaning for health care. Research results will not be returned to you because they would not be relevant to your health care.

What happens if I am injured or hurt during the study?

If you have a medical emergency during your participation on this study, you should go to the nearest emergency room. You should contact the Principal Investigator or Emergency contact listed on page one of this form. You may also contact your own doctor, or seek treatment outside of the University of Pennsylvania. Be sure to tell the doctor or his/her staff that you are in a research study being conducted at the University of Pennsylvania. Ask them to call the telephone numbers on the first page of this consent form for further instructions or information about your care.

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them. There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury.

Financial compensation for such things as traveling, parking, lost wages, disability or discomfort due to injury is not available.

You will not lose any of your legal rights when you sign this form.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by your physician, the study Sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions before T cell infusion.
- The manufacture of your CAR T cells was not sufficient or successful.
- The Sponsor, the study Principal Investigator, or the Food and Drug Administration (FDA) has decided to stop the study.

If you decide not to continue participating, you are free to leave the study at any time. Withdrawal will not interfere with your future care. If you decide to withdraw from the study before its completion, it may be more difficult to check you for long-term side effects that might develop from the CD4 CAR+CCR5 ZFN modified T cells.

However, even if you decide to discontinue your participation, we would like to continue to follow you to ensure your wellbeing. We will ask you to participate in a separate long-term follow-up study where your health will continue to be monitored for a total of up to 15 years after your T-cell infusion. You should also inform all future doctors and healthcare providers that you were on a study and received CD4 CAR+CCR5 ZFN modified T cells.

Who can see or use my information? How will my personal information be protected?

The investigator and staff involved with the study will have access to your personal health information collected for the study and will keep it strictly confidential.

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. Only the minimum necessary data will be provided to the people/entities named below and when possible participants will be identified with a unique study identification number. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. This study is being overseen by the Food and Drug Administration (FDA), who may also review your research records.

Electronic Medical Records and Research Results

What is an Electronic Medical Record and/or a Clinical Trial Management System?

An **Electronic Medical Record (**EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

A clinical trial management system (CTMS) is used to register your information as a participant in a study and to allow for your research data to be entered/stored for the purposes of data analysis and any other required activity for the purpose of the conduct of the research.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, information related to your participation in the research (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS. Information related to your participation in clinical research will also be contained in the CTMS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any information produced from your participation in this research study. The creation of this EMR is required for your participation in this research study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). Information related to your participation in the research study (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.

Once placed in your EMR or in the CTMS, your information may be accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc.).

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*. 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 Web site at any time.

What information about me may be collected, used or shared with others?

The following personal health information will be collected, used for research, and may be shared during your involvement with this research study:

- Name, address, telephone number, e-mail address, date of birth
- Personal and family medical history, allergies; prior hospital admission/discharge information
- Current and past medications or therapies
- Social security number
- Medical record number
- Information from a physical examination that generally also includes blood pressure reading, heart rate, breathing rate and temperature
- Results of tests and procedures you will undergo during this research study as described in this informed consent form

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- Do the research
- Oversee the research
- See if the research was done right
- Evaluate and manage research functions

Who may use and share information about me?

The following individuals may use or share your information for this research study:

- The Principal Investigator (study doctor) and his study team.
- Authorized members of the workforce of the University of Pennsylvania who may need to access your information in the performance of their duties (for example: for research oversight and monitoring, to provide treatment, to manage accounting or billing matters, etc.).
- Authorized members at the University of Pennsylvania, School of Medicine who coordinate this study and support research operations.
- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB.

Who, outside of the School of Medicine, might receive my information?

- The funding sponsor (National Institutes of Health) and its authorized agents

Regulatory and safety oversight organizations

- The Food and Drug Administration
- The Office of Human Research Protections
- The Office of Biotechnology Activities and their committees overseeing gene therapy research
- The Study Data and Safety Monitoring Board
- Public Health agencies and other governmental agencies (including non-U.S.) as authorized or required by law

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board gives permission
- As permitted by law

Can I change my mind about giving permission for use of my information?

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the Principal Investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

What may happen to my information and samples collected on this study?

Collection of Research Specimens

As outlined above, you will have research samples (or specimens) collected as part of your participation in this study. Depending on the type of specimen, these samples may be labeled with identifiable information. It is possible that your specimens may be used to establish products that could be patented, licensed, or sold, which could make money for others. If this happens, there are no plans to tell you or provide financial compensation to you or your family. Most uses of biospecimens do not lead to commercial products or profit to anyone.

Whole genome sequencing will not be conducted on your samples as part of the planned study analysis. However this may be performed as part of future use of your specimens (described in more detail below). Whole genome sequencing involves analyzing your entire personal genetic code.

Future Use of Data and Specimens

Blood, remaining unmanufactured cells (from your apheresis collections), unused manufactured CAR T cells or other samples obtained from you while you are participating in this study will be stored indefinitely and used for research purposes by researchers/collaborators at the University of Pennsylvania. These samples may be used for future research, to conduct new laboratory studies, or be sent to other researchers for collaborative studies, including researchers at for-profit agencies. There are no plans to tell you about any of the specific testing that will be done. This future research may include genetic testing and/or whole genome sequencing. Whole genome sequencing involves analyzing your entire personal genetic code. Please refer to the risks section of the consent for the risks of genetic testing.

You will not be given the results of any future testing performed on your samples. You will also not directly benefit from any future research with your specimens. However, it is possible this research may help others by improving our understanding of your disease and possible treatments.

Specimens used for future research will be stored in a coded fashion. Coded means that all direct identifiers (name, initials, medical record numbers) have been removed. However your samples will still include your unique subject identification number and may be linked back to information/data that was collected from you as part of this study (i.e. disease response, safety, diagnosis, etc). However, the information shared with other researchers will be de-identified. It will not be possible for future researchers to

identify you. The future use of your samples only applies to the samples collected on this study.

If you have any questions about the storage of your samples, or would like to withdraw your permission to use and store these samples at any time, please contact the study doctor, Dr. Tebas at (215) 662-6932. However, any samples that have already been used for research purposes will be retained. After all research analysis on these samples is complete, these samples may be destroyed at any time without notice.

Who can I call with questions, complaints or if I'm concerned about my rights as a research participant?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research participant, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached, or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs at the University of Pennsylvania by calling (215) 898-2614 with any concerns or complaints.

Financial Conflict of Interest

The University of Pennsylvania has a significant financial interest in the study drug being evaluated in this research protocol. In the event that the study drug proves to be effective, the University of Pennsylvania will likely receive significant financial benefit.

In addition, one of the investigators involved in this study also has significant financial interests related to this research. Specifically:

Dr. James Riley (a scientific advisor for this study) has financial interest in the study drug that is being evaluated in this trial. As a result of his financial interest, if the study drug proves to be effective, Dr. Riley will likely receive significant financial benefit.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania Health System and the School of Medicine to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania Health System and the School of Medicine to disclose that personal health information to outside organizations or people involved with the operations of this study.

You will be given a copy of this consent form and Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study.

Name of Participant (Print)	Signature of Participant	Date
Name of Person Obtaining Consent (Print)	Signature of Person Obtaining Consent	Date

List of Terms Used in the Consent:

1) ***Apheresis*** - Apheresis is the removal of white blood cells from your blood. In order to collect your cells, you must have a needle inserted into each arm. Your blood will be drawn through sterile tubing into a sterile bowl inside a machine that separates your white blood cells from the rest of your blood. Your cells will be collected into a sterile collection bag. During the procedure, the machine works in cycles. In one cycle the machine is drawing blood into the sterile bowl to collect your cells. In the second cycle the machine is returning your red blood cells and platelets (cells that help your blood clot) back to you. The procedure ends with the machine in the return cycle. A solution called acid-citrate-dextrose (ACD) and salt solution (saline) is used during the process to prevent your blood from clotting within the tubing of the machine. A small amount of the solution will also be returned to you along with your red blood cell and platelets. The procedure usually takes between 2-3 hours to complete and trained personnel in the apheresis unit supervise the procedure.

2) ***Blood draw*** – blood will be taken from a vein in order to monitor your health and for research.

3) ***Electrocardiogram*** – An electrocardiogram (EKG or ECG) is a test that checks for problems with the electrical activity of your heart. An EKG translates the heart's electrical activity into line tracings on paper. The spikes and dips in the line tracings are called waves. During an EKG, several electrodes are attached to the skin on each arm and leg and on your chest. These are hooked to a machine that traces your heart activity onto a paper. If an older machine is used, the electrodes may be moved at different times during the test to measure your heart's electrical activity from different locations on your chest.

4) ***Examination of your veins*** – a nurse or doctor will look at the veins in your arms to make sure you have good enough veins to undergo a procedure (called apheresis).

5) ***Medical history*** – the doctor or study nurse will ask you about all previous medical conditions, past and current medications you may be taking, and participation in any prior clinical trials.

6) ***Physical examination*** – temperature, blood pressure, heart rate, respiratory rate, blood oxygen levels (these are also called vital signs), current medications (including over the counter medication and those prescribed by a doctor) and a doctor or nurse will examine you and ask you how you are feeling.

7) ***Pregnancy Test –*** collection of urine or blood to determine if a woman is pregnant.

8) ***T-cells*** – Type of white blood cell that helps fight against infection; also known as T-lymphocytes.

9) ***Urinalysis*** – collection of urine for monitor your health

10) ***Urine Pregnancy Test –*** collection of urine to determine if a woman is pregnant

11) ***Vital Signs*** – temperature, blood pressure, heart rate, respiratory rate and possibly a pulse ox (blood oxygen levels). Normally done during a Physical Exam.