

Cover Page

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1.) Protocol for NCT 07193875

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Safety, Tolerability, and Efficacy of Efavirenz (EFV) Intensification on the HIV-1 reservoir

Version 13. May 31, 2024

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46)
- 21 CFR 312
- ICH GCP E6
- Completion of Human Subjects Protection Training
- NIH Clinical Terms of Award

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this clinical study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Signed: _____ Date _____
Investigator, Washington University

Signed: _____ Date _____
Investigator, Washington University

Signed: _____ Date _____
Investigator, Washington University

POTOCOL TEAM ROSTER

Principal Investigators:

[REDACTED]

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Safety, Tolerability, and Efficacy of Efavirenz (EFV) Intensification on the HIV-1 reservoir

PROTOCOL SUMMARY

Subjects: Participants with HIV, specifically with a HIV VL <500 for at least 26 weeks, who are not currently on an NNRTI and with no documented NNRTI resistance

Study Site: Infectious Disease Clinical Research Unit Washington University School of Medicine St. Louis

Study Duration: 2 years (4 months (120 days) of participant participation)

Number of subjects: 12

Subject Participation Duration: 6 months (180 days)

Description of Study Design: To evaluate the safety and tolerability of efavirenz (EFV) intensification on the HIV-1 reservoir. Participants with well controlled HIV, specifically with a HIV VL <500 for at least 26 weeks will be eligible. Prior to enrollment, we will prescreen individuals to ensure they do not have a polymorphism in CY450 which results in rapid metabolism of the study drug efavirenz. Leukapheresis will be collected at baseline. Participants eligible to participate will begin taking Efavirenz in addition to their baseline combination antiretroviral therapy. Blood (120ml) will be collected at day 60 for cell associated HIV RNA and HIV DNA assessments. Safety labs (CBC, monitoring chemistries and CD4, HIV VL) and one additional tube for future potential studies will be collected at monthly blood draws on days 30, 60 and day 90. Follow-up Leukapheresis will be collected at completion of study, between day 100-120, based on scheduling. Monthly blood draws will also be used to evaluate pharmacokinetics (PK) and ensure therapeutic levels of Efavirenz. At the completion of the 120 day course of efavirenz, participants will stop efavirenz but continue their baseline HIV regimen.

Primary

1. To determine the safety and tolerability of EFV intensification to HIV-infected participants on a stable antiretroviral therapy regimen with HIV-1 RNA levels <50 copies/mL.
2. To assess changes in plasma viremia using single copy HIV-1 RNA assay before, during, and after EFV intensification.
3. To assess changes in cell-associated unspliced and spliced HIV-1 RNA and total HIV-1 DNA in different subsets of blood and LN CD4⁺ T cells before, during, and after EFV intensification.
4. To determine the frequency of intact pro-viral DNA in different subsets of blood T cells before, during, and after EFV intensification.

Secondary

1. To determine frequency of replication competent viruses in blood CD4⁺ T cells by QVOA before, during, and after EFV intensification.
2. To assess pyroptosis by evaluating proportion of lymphocytes undergoing caspase-1 activation before, during, and after EFV intensification using FLICA Caspase-1 dye.
3. PK data on EFV.

Exploratory

1. Assess changes in cellular immune activation by evaluating proportion of CD4⁺ and CD8⁺ T cells co-expressing activation markers CD38/HLA-DR and CD69/CD25 before, during, and after EFV intensification.
2. HIV specific T cell responses before, during, and after EFV intensification by ELISpot.
3. Determine if CYP2B6 metabolism characterization correlates with efficacy of Efavirenz in activating the CARD8 mechanism and likelihood of experiencing side effects

BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

People living with HIV can achieve control over their infection with antiretroviral therapies (ART); approximately 90% of treatment naïve patients can have normalization of their CD4 and achieve undetectable virus in plasma with improved life expectancy if they take daily ART. When treatment is interrupted, viral replication resumes (1). The failure of ART to cure HIV results from the latent reservoirs of HIV, which are believed to be in resting memory CD4⁺ T cells (2-6), and possibly tissue macrophages (7). The latent reservoir is dynamic, and the proportion of actively replicating cells are shaped by viral cytopathic effects (CPE), immune clearance by cytotoxic T cells, or antibody Fc-dependent cell killing mechanisms (8). We aim to intensify HIV therapy with a medication that will enhance recognition of the infected cells by the immune system allowing for improved clearance.

One challenge of clearing the reservoir is the within-host diversity of HIV-1, which allows rapid selection of antibody and T cell escape variants (9-14). In patients on ART, immune escape variants are either already achieved in the latent viral reservoirs or rapidly emerge after treatment interruption (15-18). In addition, CD4⁺ T cells and macrophages harboring latent HIV-1 are resistant to CD8⁺ T cells and NK cells mediated cytotoxicity due to a variety of mechanisms (19-22). Therefore, it is very important to develop novel strategies to overcome immune escape and trigger cell killing via conserved immutable components of HIV.

The host immune system utilizes germline-encoded pattern-recognition receptors (PRRs) to detect microbial products. A set of intracellular PRRs characterized by the presence of a caspase recruitment domain (CARD) or a pyrin (PYD) domain co-oligomerize with pro-caspase-1 and form high-molecular weight inflammasome complexes upon sensing of their cognate ligand (23). Inflammasome assembly in response to cytoplasmic microbial or danger signals leads to caspase-1 (CASP1) activation and pyroptosis, an inflammatory form of programmed cell death. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as efavirenz (EFV) and rilpivirine (RPV) can promote dimerization of the Gag-pol precursor protein and cause premature intracellular activation of the viral PR (24-26). Recent work from the Shan lab has shown that NNRTIs induce early activation of the HIV protease resulting in pyroptosis of infected cells in a CARD8 dependent fashion. This mechanism takes advantage of an essential viral protein function and will be able to function despite pre-existing or future viral diversity (27).

We propose to provide treatment intensification with EFV to patients to allow for activation of the CARD8 inflammasome and clearance of the HIV-1 reservoirs. Subpopulations of CD4⁺ T cells including central memory (T_{CM}), transitional memory (T_{TM}), and effector memory (T_{EM}) cells comprise the largest proportion of HIV DNA (28). Blood T_{EM} and T_{TM} cells are the main contributors to active HIV transcription in patients on suppressive ART (29, 30). Similarly,

transcriptionally active HIV was often found in tissue CD4⁺ T cells, especially in lymph nodes (31, 32). Our hypothesis is that EFV intensification will eliminate viral reservoirs with active HIV transcription.

POTENTIAL RISKS AND BENEFITS

Potential risks:

The investigators believe that the health risks to Human Subjects from participating in the proposed studies are minimal.

The blood collection procedure carries a risk of pain (typically mild pain and very temporary), vasovagal symptoms (e.g. temporary light headedness or low blood pressure), bleeding, bruising, redness or swelling and, very rarely, infection. These risks are very small, and phlebotomy will be performed by registered physicians, experienced clinical research nurses or accredited phlebotomist to minimize any potential risk or discomfort.

The risks of Leukapheresis include bruising or infection at the site of the needle insertion. Discomfort and some pain at the site of the needle, which will be in place for several hours, may occur. The anticoagulant solution in the Leukapheresis machine prevents blood clotting but it may cause tingling sensations around the mouth/hands, or other parts of the body. Chills, muscle cramps, nausea, and/or vomiting may occur, but this does not happen often. There is a very small risk that the anticoagulation will lead to bleeding.

Rarely, blood pressure may fall, and lightheadedness or fainting may occur. Seizures may occur rarely. Shock, irregular heartbeats, and death have been reported, but are uncommon and usually due to an underlying illness rather than the Leukapheresis procedure. There is a remote possibility of disrupting the red blood cells (called hemolysis) due to a malfunction of the machine; however, this is rare and is carefully monitored. In the event of hemolysis, the procedure would be discontinued. Infection and loss of red blood cells due to leakage or breakage of the plastic tubing or containers may occur and thus prevent the return of the red blood cells to your body

Although the machine is equipped with an air detector to prevent air bubbles, there is a remote possibility of an air bubble entering your body. The consequences of the event could be severe and result in death. There is a risk of an allergic reaction to Acid-citrate-dextrose (ACD).

There is an added burden of taking an additional medication for four months. Specific risks of efavirenz include impaired concentration, abnormal dreams, rash, dizziness, nausea, headache, fatigue, insomnia and vomiting. Other risks include hepatotoxicity, increased risk of convulsions, lipid elevations and fat redistribution.

Financial risks are largely related to time for clinic visits and travel costs. Subjects will not be charged for any of the services or procedures provided as a part of the study, although they may have charges for standard of care medical visits which may occur during the study or as a result of information obtained as part of the study.

Participants will be fully consented and made aware of the potential risks associated with their participation in the study and have the knowledge that they can discontinue the study at any time. Each subject will be monitored carefully and appropriately and will be instructed to contact the study team promptly upon noticing any complication or health issues. Should this occur, subjects' health history will be reviewed by the study team.

All subjects asked to participate in the clinical studies will be advised that their participation in the studies is entirely voluntary, that they can choose to discontinue participation at any time and that this will not negatively impact on their access to routine health care.

There may be other unknown risks, discomforts, or side effects.

Other risks to staff and research participants

No risks are anticipated aside from those covered by universal precautions.

Known Potential Benefits

There is no known potential benefit but knowledge can potentially be gained which in the future may lead to an HIV cure.

STUDY DESIGN

This study is a prospective study of participants with well controlled HIV (VL <500) to assess the safety and efficacy of efavirenz intensification on reducing the HIV-1 reservoir.

Participants will be approached by phone, email or at BJH/WashU to determine whether they are interested in participating, and screened. If interested, participants will be scheduled for a study visit.

At the study visit, participants will be consented to the study. Subjects will undergo clinical assessments under the supervision of the study PI to determine their eligibility to participate in these studies. Subjects will also be interviewed by trained clinical research staff using standardized data collection forms, to providing detailed demographic, clinical and medication data, particularly focusing on their past antiretroviral regimens. Baseline blood tests including Leukapheresis to establish the HIV reservoir at baseline will be collected in the 60 days prior to regimen intensification. Patients will be started on efavirenz and maintained on it from day 0-120. At follow up visit around day 60, 120ml of blood will be collected to assess plasma viremia with single copy HIV RNA assay as well as cell-associated HIV-1 RNA, total HIV-1 DNA, intact proviral DNA, CD4 and efavirenz levels. Additional visits for monitoring chemistries will be performed monthly (day 30, 60 and day 90). A second Leukapheresis will be performed at the completion of the study between days 100-120, prior to Efavirenz discontinuation. This will help determine the difference in the latent viral reservoir.

INCLUSION

1. At least 18 years of age
2. Diagnosis of HIV as determined by any one of the following
 - Documentation of HIV diagnosis in the medical record by a licensed health care provider;
 - OR HIV-1 RNA detection by a licensed HIV-1 RNA assay demonstrating

- >1000 RNA copies/mL;
- OR any licensed HIV screening antibody and/or HIV antibody/antigen combination assay confirmed by a second licensed HIV assay such as a HIV-1 Western blot confirmation or HIV rapid Multispot antibody differentiation assay.

NOTE: A “licensed” assay refers to a US FDA-approved assay, which is required for all IND studies. Non-US sites are encouraged to use FDA-approved methods; if not available, then each non-US site must use an assay that has been certified or licensed by an oversight body within that country and validated internally.

WHO (World Health Organization) and CDC (Centers for Disease Control and Prevention) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment.

3. Documentation of at least two historical HIV-1 RNA measurements <500 copies/mL while on ART obtained by standard assay.
4. No known non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance mutations.
5. Currently on a stable regimen composed of integrase strand transfer inhibitors (INSTI) and nucleoside reverse transcriptase inhibitors (NRTI). Receiving the current regimen for at least 90 days prior to study entry with no intention to change for the duration of the study.
6. HCV antibody negative result within 90 days prior to study entry or, for study candidates who are HCV antibody positive (based on testing performed at any time prior to study entry), a negative HCV RNA result obtained within 90 days prior to study entry.
7. Negative HBsAg result obtained within 90 days prior to study entry or a positive HBsAb result at any time prior to study entry.
8. For females of reproductive potential, negative serum or urine pregnancy test (latter with a sensitivity of ≤ 25 mIU/mL) at the screening visit, pre-entry visit within 30 to 0 days prior to study entry, and at entry, by any US laboratory that has a CLIA certification or its equivalent.

Note A: Reproductive potential is defined as:

- Girls who have reached menarche or
- Women who have had menses within the past 12 months and who do not have an FSH >40 IU/L or
- Women who have had menses within the past 24 consecutive months if an FSH measurement is not available
- Women who have not undergone surgical sterilization (eg, hysterectomy, or bilateral oophorectomy, or bilateral salpingectomy).

Note B: Confirmation of the lack of reproductive potential is required.

Written documentation or oral communication from a clinician or clinician’s staff documented in source documents of one of the following must be provided: Physician report/letter, operative report or other source documentation in the patient record, discharge summary, laboratory report of azoospermia (required to document successful

vasectomy), FSH measurement elevated into the menopausal range (as established by the reporting laboratory).

Note C: If the female candidate cannot provide written proof of a male partner's vasectomy status, the oral report of her partner's status should be written into the source documents.

9. Female candidates of reproductive potential must refrain from participating in active attempts to become pregnant, and, if participating in sexual activity that could lead to pregnancy, must agree to use at least two reliable forms of contraception that are non-estrogen based.

Acceptable forms of contraception include:

- Condoms (male or female) with or without spermicidal agent
- Diaphragm or cervical cap with spermicide
- Non-hormonal or progestin-only containing intrauterine device (IUD) (eg, Mirena, Implanon, Nuva Ring)
- Tubal ligation
- Non-estrogen containing formulations of hormonal birth control drugs, given by pills, shots, or placed on or under the skin, for at least 90 days prior to study entry

NOTE: Providers and candidates/participants should be advised that not all contraceptive choices listed above can prevent HIV transmission and that some may actually increase the risk of HIV acquisition. Participants who are sexually active with HIV negative or unknown HIV serostatus partners should be advised that they need to consider effective strategies for reducing the risk of HIV transmission, as well as meeting the requirement for effective contraception during their participation in the study. Participants should discuss contraceptive choices and HIV risk reduction methods with their health care provider.

Females who are not of reproductive potential are not required to practice contraception.

10. Able to provide informed consent

EXCLUSION

1. Individuals who are incarcerated.
2. Any condition that in the opinion of the investigator would interfere with the proper conduct of the trial
3. Untreated depression, defined as a PHQ-9 > 15 at time of enrollment
4. Known prior NNRTI resistance, or INSTI resistance. Genotype testing will not be done at time of enrollment.
5. Prior protease inhibitor (PI) regimens are allowed, but participant must not currently be on a PI.
6. Any evidence of liver injury or other underlying liver abnormality, including baseline elevation in AST, ALT, ALP, or Tbili outside of normal limits based on clinical standards

7. A history of a medical condition resulting in impaired immunity other than HIV (such as cancer, particularly leukemia, lymphoma, use of immunosuppressive or antineoplastic drugs or X-ray treatment). Persons with previous skin cancers or cured non-lymphatic tumors are not excluded from the study.
8. History of any chronic medical conditions that are considered progressive or uncontrolled and have required hospitalization in the past 3 months (ex, diabetes, heart disease, lung disease, liver disease, kidney disease, gastrointestinal diseases and uncontrolled hypertension).
9. Chronic, acute, or recurrent infections that are current and serious, in the opinion of the site investigator, for which the participant has not completed at least 14 consecutive days of therapy within 30 days prior to study entry and/or is not clinically stable.
10. Active autoimmune disorders including but not limited to inflammatory bowel diseases, scleroderma, severe psoriasis as determined by the site investigator, systemic lupus erythematosus, rheumatoid arthritis, and optic neuritis.
11. History of myocardial infarction (MI) within 6 months prior to study entry, history of QTc prolongation (defined as ECG with QTc intervals > 490 ms) at any time prior to study entry, New York Heart Association (NYHA) class III or IV heart failure at any time prior to study entry, or family history of prolonged QTc syndrome.
12. Breastfeeding patients as well as those whom are pregnant or plan to become pregnant during period of the study.
13. Use of immunomodulators (eg, interleukins, interferons, cyclosporine), HIV vaccine, systemic cytotoxic chemotherapy, or investigational therapy within 60 days prior to study entry.
NOTE: Study candidates receiving stable physiologic glucocorticoid doses, defined as prednisone ≤ 10 mg/day, will not be excluded. Study candidates receiving inhaled or topical corticosteroids will not be excluded.
14. Active illicit drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.
15. Acute or serious illness requiring systemic treatment and/or hospitalization that is not resolved within 30 days prior to entry.

Handling of Withdrawals

Subjects are free to withdraw from the study at any time.

Subjects may be taken off study without their consent if the study doctor determines that it is in the subject's best interest not to continue to participate in the study. In addition, the study doctor may remove a subject from study participation if the subject is unable to complete the required study procedures, or if the study is stopped by the institution, the sponsor, or the Food and Drug Administration (FDA) or other health authorities. If the subject is removed from the study, the Principal Investigator or designee will contact the participant to discuss the study stopping procedures.

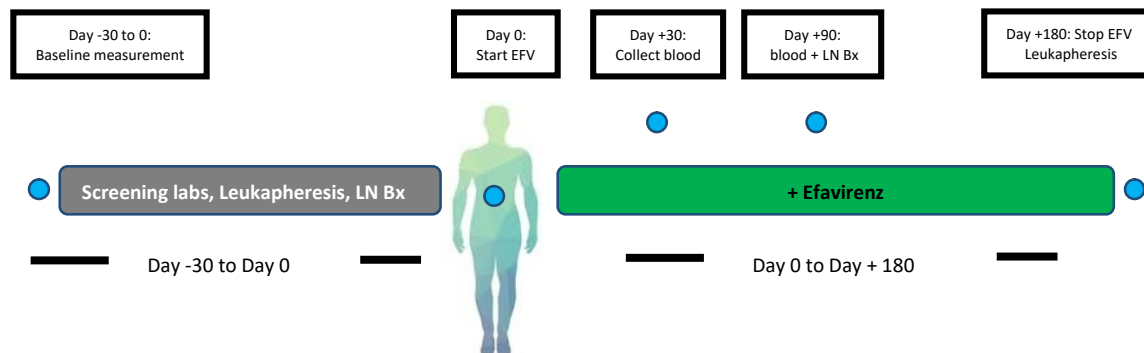
Participants who withdraw, are withdrawn or terminated from the study, or are lost to follow-up after study enrollment visit will not be replaced.

STUDY PROCEDURES

Eligibility

Participants will be screened by phone, in person or email for interest in the study, and confirm that they are not currently on an NNRTI and have been well controlled for at least 26 weeks with a HIV VL <500.

Schedule of Evaluations



Evaluations	Day (-60 to 0)	Day (-30 to 0)	Day 0	30 days (+/- 2 d)	60days (+/-2d)	90 days (+/- 2 d)	Day 100-120	120 days (+/- 7d)
Review medical history	X		X	X		X		X
Review concomitant meds	X		X	X		X		X
Symptom Review	X		X	X		X		X
Screening Labs	X							
Vein evaluation for apheresis prior to initial Leukapheresis + EFV CYP2B6 eval	X							
Start Efavirenz			X					
Safety Labs	X			X	X	X		X
Stop Efavirenz								X
Leukapheresis-1 (150ml product)		X						
Additional Blood /plasma collection		20ml		20ml	120m L	20 ml		20ml
Leukapheresis-2 (150ml product)							X	
Visit duration	2hr	4-5hr	1hr	1hr	1hr	1hr	4-5hr	2hr
Pay to participant Leukapheresis		\$300					\$700	
Pay to participant for Study visit	\$25		\$25	\$25	\$25	\$25		\$25

Screening labs: CD4, VL, CMP, CBC

Safety labs: CD4, VL, CMP, CBC

Additional blood draw with pheresis for plasma collection:

Additional blood collection of 120mL on day , 60: blood for viral outgrowth assay and cell free DNA assay

Additional visits for monitoring chemistries will be performed on day 30, 60, 90.

Additional tube collected for future potential studies (20mL): day 30, 60 and 90

Study Visits

Eligible participants will be consented at the baseline visit prior to any research procedures. At baseline, data will be collected both from the participant and medical record about demographics, past medical history, HIV VL, CD4, concomitant medications, HIV medication history, and disease course [prior opportunistic infections, when they were diagnosed, how long post diagnosis were they started on ART, any treatment interruptions]. Baseline blood work, Leukapheresis will be performed prior to initiation of efavirenz.

At subsequent visits, participants will be asked about any new symptoms or adverse effects of the new medication. Blood (120ml) will be collected at day 60 for cell associated HIV RNA and HIV DNA assessments. Safety labs (CBC, monitoring chemistries and CD4, HIV VL) and one additional tube for future potential studies will be collected at monthly blood draws on days 30, 60 and day 90. At day 100-120, a completion Leukapheresis will be performed.

Study Duration

Total duration of participation in the study will be up to 120 days.

SAFETY ASSESSMENTS

The subjects will be carefully monitored for potential side effects at their planned study visit. In addition, study subjects will be asked to contact the study team if they feel unwell or experience any worsening of their health.

SAMPLE SIZE AND POWER CALCULATION

As this protocol is just to establish safety and efficacy of combination therapy there is no sample size determination made.

SOURCE DOCUMENTATION

All source documents will be kept in an appropriately secure office in a locked high density filing system in a locked office.

QUALITY CONTROL

All eligibilities and ICFs and a portion of the study case report forms (no less than 10%) will be audited by the ID CRU clinic quality management personnel per the ID CRU clinic SOPs.

ETHICS AND PROTECTION OF HUMAN SUBJECTS

Once the study is approved by the Washington University Human Research Protection Office (HRPO), recruiting and screening will begin for the study. All subjects are required to read English, understand and sign the informed consent document.

Adverse event monitoring will be performed and reported via Toxicity scale 2.1

DATA HANDLING AND RECORD KEEPING

The clinical data on the participants will be maintained at the ID CRU clinic in a locked file cabinet. The data on the clinical samples for immunological and genetic testing will be de-identified and will only be identified with a unique code number and will be maintained in ID CRU, or laboratories of sub-investigators. The links to the unique codes will be stored at the ID CRU and will not be available to the laboratory personnel. Data will be stored and analyzed using Washington University's RedCap database.

The study records will be maintained up to ten years after the completion of the study.

PUBLICATION POLICY

The PI and co-investigators will participate in manuscript preparation and submission to journals.

LITERATURE REFERENCE

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