TITLE OF STUDY

Statin down-modulation of monocyte / macrophage Activation for HIV-1 Associated Neurocognitive Disorders (HAND) treatment

IRB PROTOCOL#

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Abstract

HIV associated neurological disorders (HAND), are a major problem even in ART treated people. HAND results from chronic inflammation which is largely attributed to expansion and activation of monocytes. These activated monocytes, some of which also carry virus to the brain, invade the CNS and release cytokines / chemokines resulting in further recruitment of monocytes, as well as release viral proteins which injure neurons and cause activation of other brain cells. Persistent monocyte/macrophage activation is thus a potential critical target for adjunctive therapy to treat or prevent HAND. We therefore propose to study the effects of a statin drug (Atorvastatin), which has anti-inflammatory functions, on the monocyte activation status in vitro and in ART treated HIV+ individuals. We will also define monocyte gene expression patterns in these subjects before and after statin treatment.

Eligibility: Enrolled subjects will be on anti-HIV therapy, viral load less than 200 copies/ml for more than six months at the time of screening.

Intervention:
1) Thirty subjects will be treated either with placebo or with the drug Atorvastatin. Those on PI based HAART regimen will be administered 10mg/day X 2weeks and then 20mg/day for 10 weeks. This is followed by a washout phase and then a second treatment period with Atorvastatin or placebo for the same duration as before. This will again be followed by a washout phase. Subjects on non-PI / non-NNRTI based HAART regimen will be administered 20mg/day X 2weeks and then 40mg/day X 10weeks. A similar treatment schedule will be followed as above. Subjects on NNRTI based HAART regimen will be administered 40mg/day X 2weeks and then 80mg/day X 10weeks. All subjects will undergo neuropsychological tests during the treatment period.

1) At specific time points during the study period, blood will be drawn to study various immune and virological parameters.

In a sub-study of 16 subjects during the treatment period, each subject will also undergo 2 lumbar puncture procedures to assess anti-inflammatory marker levels in the CSF, in addition to the above-mentioned tests.

OBJECTIVES

Overall objectives

Our objectives are based on the hypothesis that Atorvastatin treatment will reduce the inflammatory and activated phenotype and function of monocytes which have been linked to HIV associated neuropathogenesis and occur in HIV infected subjects despite ART. In this study we propose to

1) determine how Atorvastatin modulates monocyte activation, intracellular signaling

pathways and functions implicated in the pathogenesis of HAND in vitro
2) define the effect of Atorvastatin on monocyte activation in HIV infected / ART treated subjects in a double blind, placebo controlled crossover study
3) define gene expression patters of monocyte activation before and following statin treatment
4) assess Atorvastatin effects on CNS immune activation markers and neurocognitive function in ART treated subjects.

Secondary Objectives (optional PET substudy)

1.To evaluate the effects of 12 weeks of atorvastatin treatment therapy in arterial wall inflammation measured with FDG-PET
2. To evaluate the effects of brain dysfunction /inflammation as measured by FDG-PET in HIV infected individuals with or without treatment with atorvastatin
3. To evaluate the levels of inflammation throughout the body and in multiple organs as measured by FDG-PET.

Primary outcome variable(s)
1) Peripheral blood monocyte surface markers CD16; CD14; CD163; CCR2;

2) Plasma levels of monocyte associated inflammatory cytokines and chemokines: MCP-1; sCD14

3) Monocyte gene expression patterns in ART treated HIV+ subjects.
Secondary outcome variable(s)
1) Monocyte Tissue Factor (TF); sCD163; D-dimer and hsCRP
Background

HAND (HIV-associated neurocognitive disorders) includes asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorders (MND) and, most severe, HIV-associated dementia (HAD). Widespread use of antiretroviral therapy (ART) in the developed world has led to a marked decrease in HAD. In contrast, ART does not prevent MND & ANI, which are increasing in prevalence as people live longer and now affect 25-50% of treated individuals. Thus, despite great success of ART, HAND remains a major long term problem for treated individuals and particular threat in high HIV prevalence areas of the developing world where the increasing availability of treatment is extending lives, meaning large segments of the population are at high risk for neurocognitive impairment. Thus, there is great need for adjunctive neuroprotective strategies, especially approaches that will be widely available, economically feasible, safe & suitable for longterm use. The only effective specific strategy until now has been maximizing the degree of intra-CNS viral suppression by ART (CNS Penetration Effectiveness; CPE). While critical to maximize neurocognitive benefit this clearly does not eradicate residual immune activation & inflammatory mechanisms driving HAND.

We propose to address residual monocyte/macrophage activation that is the upstream driver of neurodegeneration. HAND is a disease of both CNS and peripheral blood M/M activation: Neuronal injury in HAND results from the accumulation of activated

monocyte/macrophage lineage cells (M/M) in the CNS, some of which are infected, that release cytokines, small molecule excitotoxins or viral proteins that lead to neurodegeneration. While HAND is typically a manifestation of later disease, studies of HIV-1 in CSF & animal models with SIV show that HIV enters the brain early.

In untreated HIV infection neurocognitive dysfunction is strongly associated with the level of viral replication within (or viral penetration into) the CNS as reflected in CSF viral RNA levels. However, that correlation is imperfect and histopathological studies show the strongest association with neurocognitive function is the extent of M/M accumulation and degree of activation rather than viral antigen expression. Factors released by these activated or infected M/M that mediate neuronal damage include cytokines (TNFa, IL1b, IL6), small molecules (quinolinic acid; PAF), metalloproteinases & viral proteins (gp120, Tat, Vpr), which injure neurons directly, or indirectly via astrocytes (eg, modulation of glutamate reuptake). This accumulation of activated & activated/infected M/M in the CNS as HAND advances is linked to two interdependent mechanisms. One principal mechanism is driven by activation of monocytes in blood (push mechanism), part of the systemic generalized immune activation in HIV infected individuals. Early on it was recognized that individuals with HAND had a striking excess of monocytes in blood that express CD16 (Fc!RIII). These monocytes also express higher levels of other activation markers including CD163, CD69, CD86 & CD40 and exhibit greater TNFa & IL1b production. These cells are believed to have invasive properties that enable them to enter tissues, in particular to cross the bloodbrain barrier (BBB) and enter the CNS, where they persist as perivascular brain macrophages. CD16+ monocytes also play important role in viral entry to the CNS. Unlike macrophages, most monocytes are resistant to HIV-1 infection. However, CD16+ monocytes appear to be preferentially susceptible and the CD16+ population in blood is shown to harbor proviral DNA (even in individuals on antiretroviral therapy) and likely serve as both a blood reservoir and vector for CNS entry. In the brain, viral p24 antigen colocalizes with CD14+/CD16+ cells suggesting that this population establishes the CNS viral reservoir. Secondly, a self-perpetuating cascade is established within the CNS in which the activated and/or infected M/M release cytokines that then activate other glial cells, and chemokines that recruit additional M/M from the periphery (pull mechanism). While several chemokines are implicated (IP-10, Rantes/CCL5, MIP-1a/CCL3), most prominent is MCP-1/CCL2, which is produced by both M/M & astrocytes in the brain in HAD, and is strikingly elevated in CSF and correlated with clinical disease.

The critical role for MCP-1 in neuropathogenesis is further emphasized by an association between HAD and a polymorphism in the MCP-1 gene linked to increased MCP-1 levels & tissue monocyte infiltration. Other CSF markers elevated in HAND that reflect M/M activation are neopterin & B2 microglobulin. Microbial translocation in chronic immune activation: It is long recognized that chronic immune activation plays a central role in HIV immunopathogenesis and much progress has been made recently in understanding the mechanisms (although most interest has focused on T cell activation & systemic immunopathology, not M/M). One principal driver is viral replication itself 86. In addition, an early event in HIV infection is damage to the gut mucosa including preferential loss of mucosal lymphocytes, which leads to translocation of bacterial

endotoxin (LPS) & other products, and is an important driver of systemic immunopathogenesis. While T cell injury has been the primary focus of most studies, monocytes play a central role based on the close association with sCD14 levels, monocyte response to LPS stimulation ex vivo & other observations. Recently, microbial translocation has been linked specifically to monocyte activation and to the development of HAND thus identifying a mechanism driving this activated monocyte population. HAND on ART remains disease of persistent M/M activation & neuroinflammation: Severe dementia is now uncommon in the developed world, decreasing from an estimated 15% prevalence pre-ART to ~2% recently.

Early in the ART era it was recognized that CNS penetration effectiveness (CPE) correlated with both suppression of CSF viral RNA & neurocognitive outcome. These findings underscore the critical role of effective viral suppression, both systemically and within the CNS, in minimizing neurocognitive injury. Despite the marked reduction in HAD, milder but significant forms of HAND persist in 25-50% of ART treated subjects. In some cases, incomplete suppression linked to real world ART use may limit effectiveness, but neurocognitive impairment persists even in subjects with effective suppression. Currently, the strongest predictors of HAND in treated patients is the initiation of ART at low nadir CD4 (200-250).

Neuropathological studies show that the location & extent of involvement has changed in the era of ART but neuroinflammation remains a persistent feature. Studies of CSF inflammatory markers also reveal continued immune activation. Both neopterin & MCP-1 levels in CSF generally decline with ART. However, neopterin remains elevated above reference normal levels in more than 2/3 of subjects with prolonged viral load suppression, including 60% of those with "4 years of CSF VL below 50 copies/ml, and more than half with #2.5 copies/ml. CSF MCP-1 levels also remain elevated in a large proportion of subjects even with effective intrathecal viral control. Treatment intensification in subjects with prolonged viral suppression may not reduce residual CSF viral RNA & inflammatory markers which highlights the importance of viral expression from long term reservoirs as well as factors distinct from viral replication that drive CNS inflammation in the setting of ART, and need for strategies to target these mechanism. Persistent microbial translocation & immune activation on ART: In contrast to the high efficacy of ART at suppressing plasma viremia, reversal of chronic immune activation is much slower & often incomplete, with CD8 T cell expression of CD38, HLA-DR and other activation markers persistently elevated in a large proportion of long-term ART-treated subjects. ART does not fully reverse microbial translocation, which is linked to failure of the gut mucosal barrier to fully reconstitute. Strikingly, the persistence of chronic microbial translocation and immune activation despite ART is most frequent in individuals who begin ART late (CD4 counts 200-250) also the group most likely to exhibit neurocognitive impairment. While most studies have focused on residual T lymphocyte activation, studies now confirm persistence of monocyte-related sCD14 elevations despite prolonged ART. Furthermore, while ART may reduce the monocyte population co-expressing CD14+/CD16+, it has been reported that a CD16+/CD14low monocyte population persists.

Thus, ongoing monocyte activation, driven at least in part by incompletely reversed microbial translocation, is likely an important driver of continued neurocognitive injury despite ART. In addition to microbial translocation, low levels of residual viremia (below standard assays) are also seen in subjects with persistent immune activation (in many but not all studies). Although the residual viremia may not be sensitive to antiviral intensification and thus may not reflect ongoing rounds of replication & spread, it is believed that long lived reservoirs such as macrophages sustain viral expression, which may also contribute to residual immune activation including within the CNS.

Statins have pleiotropic immunomodulatory activity and target M/M: Statins lower cholesterol by blocking the enzyme HMG-CoA reductase, which is required for synthesis of L-mevalonate upstream of cholesterol biosynthesis. In addition, inhibition of this pathway also blocks synthesis of isoprenoids including farnesylpyrophosphate & geranylgeranylpyrophosphate, which are lipid attachments required for signaling by multiple intracellular molecules. As a result, multiple cell signaling molecules (particularly small GTPases Rho, Rac, Cdc42) and their downstream pathways are modulated (termed pleiotropic statin effects). Inflammation plays a central role in atherosclerosis, and extensive evidence shows that statins potently downregulate this inflammation.

Clinical evidence that statins benefit extends beyond that attributable to cholesterol lowering include the rapidity of statin action in clinical trials (often within days) and recognition that benefit is not necessarily related to baseline cholesterol levels or degree of cholesterol reduction. M/M are principal inflammatory cells in both blood & vascular lesions of atherosclerosis and either source or target of many of the mediators implicated in its pathogenesis. Extensive data support a central role for MCP-1 in monocyte chemotaxis into atheromatous lesions, and increased CD16+ monocytes are seen in circulation that may invade the vascular wall. While multiple cell types are targets of statin immunomodulation (such as endothelial & T cells), some of the most prominent effects of statin treatment are linked to reduced M/M activation including decreased plasma levels of MCP-1; reduced plasma sCD14 & neopterin levels; reduction in circulating CD16+ monocytes (which may correlate particularly well with clinical benefit); & decreased monocyte expression of CCR2 (MCP-1 receptor). Thus, M/M are central targets for statin immunomodulation, with biological effects highly relevant to activation & recruitment pathways in HAND.

Statins are immunomodulatory in inflammatory states independent of cholesterol effects: One mechanism of statin benefit in atherosclerosis is by lowering plasma lipids, which can directly injure the vascular wall and can trigger macrophage activation through lipid ingestion & foam cell formation. However, statin immunomodulation is not limited to cholesterol-linked inflammation, as they also block MCP-1 & inflammatory mediator upregulation in healthy volunteers following LPS injection, which is particularly relevant to immune activation in HAND. They also lower monocyte chemokine receptor & activation marker expression in patients with inflammatory bowel disease. In the landmark JUPITER trial statins reduced multiple inflammatory markers independent from hypercholesterolemia. Finally, numerous studies document modulation of M/M

activation in vitro & in animal models. Molecular mechanisms of statin immunomodulation in M/M include inhibition of NFkB activation, activation of the nuclear receptor PPAR-gamma and modulation of COX activity. As a result, this class of drugs is being studied for adjunctive use in inflammatory bowel disease, rheumatoid arthritis & other inflammatory disorders. Importantly, a recent report (by Dr. D. Rader, consultant on this proposal) showed that in subjects without pathological immune activation or hypercholesterolemia, statins do not suppress normal levels of inflammatory markers in plasma, or block monocyte activation ex vivo. Thus, these drugs are promising agents to target the M/M activation in HAND, particularly for subjects on ART, but to date have not been studied in this context.

Prior studies of statins & HIV: Statins are widely used in HIV infected people for lipid disorders, but only recently has attention focused on immunomodulation, and no studies have examined M/M activation or immunomodulation in ART-treated subjects. Early work suggested that statins suppress HIV-1 replication in vitro (including in M/M) via cholesterol-dependent lipid raft disruption (involved in viral entry & egress) or signaling effects, but evidence does not support a global antiviral effect in people not receiving ART. We believe effective viral suppression is & will remain the cornerstone of HAND prevention, and our focus is on statins immunomodulatory activity as adjunct therapy to ART (although as a secondary question we will address if residual monocyte associated viral DNA is reduced by statins, as may occur either by inhibiting residual low level infection in M/M or reducing the vDNA+ CD16+ population). A study of atorvastatin for 8 weeks in 7 viremic subjects not on ART found no benefit on plasma viral load, nor CSF viral load, pleocytosis & neopterin levels. However, since viral replication is a major driver of systemic & intrathecal immune activation in the absence of ART, maximizing viral suppression (systemically & within the CNS) must be the first goal of therapy and is the starting point for our study. Nevertheless, a very recent report revealed that even in subjects not on ART, atorvastatin decreased T lymphocyte activation markers despite no effect on viral load, which lends support to our hypothesis. However, M/M were not examined, and we anticipate that effects on residual activation in the setting of suppressed replication will be much greater. A very recent case-control study (published during preparation of this revision) showed significantly lower T cell CD38 levels in subjects on statins, but monocyte effects were not reported. In a cross-sectional analysis of the CHARTER cohort, Letendre et al compared subjects on statins for standard clinical indications vs those not on statins, and found that statin use in ART-treated subjects was associated with lower residual viral loads in CSF. Neuropsychological performance was not better in patients on statins; however, as acknowledged in that report many of the clinical conditions for which statins are routinely prescribed are strongly associated with neurocognitive impairment in infected individuals, including several-fold greater impairment in individuals with prior ischemic heart disease, a common indication for statin use. No controlled studies exist, and there have been no reports examining statin effects in vivo on monocytes or on residual activation persisting on ART. Thus, this highly practical & promising approach to HAND, with a strong rationale based on in vitro mechanism in vivo data in other diseases, and our preliminary data (below) may be prematurely dismissed based on findings confounded by the very indications for which statins are prescribed. Here we propose a mechanistic approach that will provide

important biomarker & M/M immunomodulation efficacy data in the setting where adjunctive therapy is most needed, as well as novel insight into the residual monocyte activation in ART/HIV infection.

Target population

We will enroll chronic HIV infected individuals who are on HAART (with no changes in treatment within 4 weeks of study entry). These individuals will have plasma viral loads less than 200 copies / ml for at least six months at the time of screening. Additionally they will not be on prior statin therapy.

Subjects enrolled by Penn Researchers

30

Accrual

We will have access to the study subjects through the UPENN CFAR clinical core, and by referral from other HIV treatment sites.

PET Substudy

A formal statistical power calculation was not conducted. The PET scan is a pilot project that will use the data from this small sample for the development of future studies. A convenience sample of 10 (with each participant receiving 4 scans) was determined as sufficient preliminary data to generate hypotheses for powered studies.

Inclusion Criteria

1. HIV-1 infection, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen, plasma HIV-1 viral load.
2. Combination ART that includes any NNRTI, a PI or an integrase inhibitor regimen for at least 6 months prior to study entry.
3. No plans to change the antiretroviral regimen in the next year.
4. Must be on the same HAART regimen with no change for at least 4 weeks prior to study entry.
5. CD4+ T-cell count > 100 cells/ul obtained within 28 days prior to study entry at any laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent.
6. Nadir CD4 $\leq$ 350
7. Screening HIV-1 RNA < 200 copies/mL by an approved ultrasensitive assay.
8. All known HIV-1 RNA levels obtained within 180 days prior to study entry are < 200 on all tests.
9. Laboratory values obtained within 28 days prior to study entry:

- Absolute neutrophil count (ANC) ≥ 1000/mm^3
- Hemoglobin ≥ 9.0 g/dL for female subjects and ≥ 10.0 g/dL for male subjects
- Platelet count ≥ 100,000/mm^3
- Creatinine ≤ 2 mg/dl
- Creatine kinase (CK) < 3 x ULN
- AST ≤ 3.0 x ULN
- ALT ≤ 3.0 x ULN

10 Screening plasma hs-CRP levels above 2mg/L from a sample obtained within 28 days prior to study entry.

11 For females of reproductive potential (women who have not been post-menopausal for at least 24 consecutive months, i.e., who have had menses within 24 months prior to study entry), or women who have not undergone surgical sterilization, specifically hysterectomy or bilateral oophorectomy or tubal ligation) will require a negative serum or urine pregnancy test within 48 hours prior to entry.

12 All subjects must agree not to participate in the conception process (e.g., active attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization), and if participating in sexual activity that could lead to pregnancy, the subject/partner must use at least two reliable methods of contraception, (condoms, with or without a spermicidal agent; a diaphragm or cervical cap with or without spermicide; an IUD; or hormone-based contraceptive), for 2 weeks before study treatment, while receiving study treatment, and for 6 weeks after receiving study treatment. As hormone-based contraceptives (oral, transdermal, or subdermal) can affect coagulopathy biomarkers, subjects who plan on using such a contraceptive during the study must be taking the same product for ≥ 4 weeks prior to screening and be encouraged to continue throughout the duration of the study if medically feasible.

13 Karnofsky performance score ≥ 80 on at least one occasion within 28 days prior to study entry.

14 Men and women ≥ 18 years of age.

15 Females must be willing to undergo pregnancy testing at every visit per SOE.

Exclusion Criteria

1 Current or past malignancy (except non-melanoma cancer of the skin).

2 Coronary artery disease (CAD) or CAD equivalent including diabetes mellitus or National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) calculated 10-year coronary heart disease (CHD) risk of > 20%

3 Pregnant or breast-feeding.

4 Active alcohol or drug use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.
5 Allergy or hypersensitivity to atorvastatin or any of its components.
6 History of myositis or rhabdomyolysis with use of any statins.
7 History of inflammatory muscle disease such as polymyositis or dermatomyositis
8 Known inflammatory conditions, such as, but not limited to, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), sarcoidosis, inflammatory bowel disease (IBD), chronic pancreatitis, autoimmune hepatitis, myositis, or myopathy.
9 Evidence of active opportunistic infections requiring treatment or neoplasms that require chemotherapy during the study period
10 Known Hepatitis C infection
11 Known coagulopathy, deep venous thrombosis, pulmonary embolism within 6 months prior to study entry.
12 NYHA class III or IV congestive heart failure.
13 Active IV drug use within 1 year prior to entry.
14 Current use of any prohibited concomitant medication
15 Previous intolerance to any statin or any of its components.
16 History of stroke
17 Known active or recent (not fully resolved within 4 weeks prior to study entry) bacterial, fungal, parasitic, or viral infections.
18 Known history of recurrent rectal and/or genital herpes simplex virus (HSV) or varicella zoster virus (VZV) infection within 12 weeks prior to study entry.
19 Serious illness or trauma requiring systemic treatment and/or hospitalization within 4 weeks prior to study entry.
20 Use of any systemic antineoplastic or immunomodulatory treatment, routine AND investigational vaccines, interleukins, interferons, growth factors, or intravenous immunoglobulin (IVIG) within 45 days prior to study entry.
21 Current use of anticoagulation therapy other than ≤ 325 mg of daily aspirin
22 Use of any lipid-lowering therapies including all statin drugs, ezetimibe, fibric acid derivatives, omega 3 fatty acids/fish oil, red yeast rice, and niacin products ≥ 1 g/day (e.g., niacin, nicotinic acid, vitamin B3) taken within 45 days prior to study entry.
23 Immunosuppressant use, such as, but not limited to, systemic or potentially systemic glucocorticoids (including nasal or inhaled steroids), azathioprine, tacrolimus, mycophenolate, sirolimus, rapamycin, or cyclosporine within 90 days prior to study entry.
24 Use of any anti-inflammatory drugs (OTC or prescription) on a daily basis.

LP Exclusion Criteria (for subjects consenting to LP sub-study)

24 Allergy to lidocaine.
25 Current use of anticoagulant therapies. Note: Use of daily aspirin for antiplatelet therapy is allowed.

Subject recruitment*

The UPENN CFAR Clinical Core will assist us in the identification and recruitment of subjects required for the study from the Clinical Core Cohort.
In addition, we have developed a flyer to hang in the MacGregor clinic as well as to distribute to other HIV care providers in the city.

Subject compensation*

The study involves one screening visit plus 10 study visits, for a total of 11 visits. Participants will be paid $50 for the screening visit and $50 for each study visit. If all study visits are attended, the maximum compensation received is $550. If a participant is enrolled in the Lumbar puncture (LP) sub-study they will also be paid $200 for each LP. If a participant is enrolled in the LP sub-study, the maximum compensation they can receive from this study is $400.

If the participant is enrolled in the PET-Scan substudy, they will be paid $50 for each scan; the maximum compensation for this study is $100.

For the study and PET-scan visits, participants will be paid cash at the time of the study visit. The compensation for the LP will be provided as a check through the Universitys accounts payable system and may take 4-6 weeks to process.

Potential Study Risks

We anticipate any risks associated with the administration of the drug will be minimal as this is a widely used FDA approved prescription drug.

The main risks associated with Lumbar Puncture are discomfort from the procedure and headache. Other associated risks are infection and bleeding.

Risks for the PET Scan Substudy:

Blood draw / Injection site risks: Local pain, bruising, bleeding, blood clot formation, and in rare instances, an infection might occur at the site of the needle stick where the blood draw and injection occur.

Allergy Risk: There is a risk of allergic or other adverse type reaction to the radiotracers but this is extremely rare. FDG is a natural sugar which has a radio-label attached. There have not been any reactions reported to FDG in the past decade, but if you were to develop an allergic reaction, we would treat it immediately with anti-allergy medicines (Benadryl, Zantac, prednisone depending on severity of the reaction).

Radio-tracer Risks: This research study involves exposure to radiation from the PET/CT scan.

Therefore, you will receive a radiation dose. This radiation dose is not necessary for medical care and will occur only as a result of your participation in the study. At doses much higher than you will receive in this study, radiation is known to increase the risk of developing cancer after many years. At the doses of radiation you will receive in this study, it is very likely that you will see no effects at all.
Risk of Incidental Findings: Unanticipated clinically insignificant or potentially significant abnormalities may be detected from the proposed imaging or non-imaging test procedures proposed in this study. Such abnormalities will be communicated to you and to your health-care providers in a timely fashion. As for any abnormalities that are detected upon clinical diagnostic procedures, there is the risk of future potentially unnecessary additional diagnostic testing or therapeutic intervention, which can be associated with various complications.

Reproductive Risks: Because this research involves exposure to radiation which can damage an unborn baby, participants should not become pregnant or father a baby while on this study. Some doctors tell PET scan patients that they should not have close contact with pregnant women, babies and young children for a few hours after their scan. Women who can become pregnant must agree to a pregnancy test (blood or urine) before each PET/CT scan. A negative pregnancy test will be mandated before a woman of child-bearing potential can participate in this study.

Potential Study Benefits

The main benefit to the subjects is financial through payment for their participation. Knowledge obtained through this study will contribute to better understanding neurocognitive diseases and treatment options in people with HIV infection. This would eventually benefit HIV infected individuals as it would identify potential adjunctive therapies for these individuals.

Participation in the PET substudy will benefit research and enable the investigators to better understand the relationship between HIV and atherosclerosis. We hope to better understand how treatment of HIV and how improved assessment of cardiovascular risk in these patients will lead to improved outcomes. Furthermore, it is hoped that the information gained from this study will validate the use of FDG-PET as a sensitive tool in detection of atherosclerosis in patients with HIV.

CLINICAL AND LABORATORY EVALUATIONS

Evaluation	Screening	Entry 0	Post-Entry Evaluations (weeks)									Premature Study Disc. Evals
			Visit Window			Washout ± 3 days	Visit Window				Final Visit ± 7 days	
			±2	±7	±2		±2	±2	±7	±2		
			2	6	12	16	18	20	24	30	36	
Documentation of HIV-1	X											

Evaluation	Screening	Entry 0	Post-Entry Evaluations (weeks)									Premature Study Disc. Evals
			Visit Window			Washout ± 3 days	Visit Window				Final Visit ± 7 days	
			±2	±7	±2		±2	±2	±7	±2		
			2	6	12	16	18	20	24	30	36	
Medical History/Medication History	X	X										
Cardiovascular Risk Assessment	X											
Clinical Assessments	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam	X										X	X
Targeted Physical Exam		X	X	X	X	X	X	X	X	X		
Alcohol and Smoking Status		X			X		X			X		
Hematology	X		X	X	X	X		X	X	X	X	X
Liver Function Tests	X		X	X	X	X		X	X	X	X	X
Lipid Panels	X	X	X		X		X	X		X	X	X
Chemistries / Glucose	X		X	X	X	X		X	X	X	X	X
Calculated CrCl	X		X	X	X	X		X	X	X	X	X
CK	X		X	X	X	X		X	X	X	X	X
Pregnancy Testing	X	X	X	X	X	X		X	X	X		X
CD4+/CD8+	X	X			X		X			X		X
hsCRP	X	X		X	X		X		X	X	X	X
D-dimer		X		X	X		X		X	X	X	X
Plasma HIV-1 RNA	X	X			X		X			X		X
Neuropsychological testing		X			X		X			X		X
Flow Cytometry		X		X	X		X		X	X	X	X
Monocyte transcriptiome analysis		X		X	X		X		X	X	X	X
Plasma luminex	X	X	X	X	X	X	X	X	X	X	X	X
Plasma ELISA/Luminex	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Atorvastatin/Placebo		X[1]	X[2]	X[2]			X[1]	X[2]	X[2]			
Pill Count for Atorvastatin/Placebo			X	X	X	X	X	X	X	X	X	X
1 - Low dose Atorvastatin / placebo (10 mg/day or 20 mg/day or 40 mg/day depending on HAART) 2 - High dose Atorvastatin / placebo (20 mg/day or 40 mg/day or 80 mg/day depending on HAART)												
Spinal Tap (subset)		X			X							X

Evaluation	Screening	Entry 0	Post-Entry Evaluations (weeks)									Premature Study Disc. Evals
			Visit Window			Washout ± 3 days	Visit Window				Final Visit ± 7 days	
			±2	±7	±2		±2	±2	±7	±2		
			2	6	12	16	18	20	24	30	36	
CSF Chemistries (Spinal Tap subset)		X			X							X
CSF Hematology (Spinal Tap subset)		X			X							X
CSF ELISA (Spinal Tap subset)		X			X							X
PET Study (optional)		X			X		X			X		X

Statistical analysis

The crossover study design enables each subject to serve as his/her own placebo-matched control, which increases power & reduces potential clinical variable confounder effects. Our primary outcomes are monocyte CD16, CD163 & CCR2 expression, and plasma sCD14 & MCP-1. Sample size calculations were based on detecting differences between statin & placebo arms in a 2x2 crossover design. While there have been no studies to establish data for HIV/ART subjects, the average differences observed with statins in vivo in other diseases are: 20% ± 32% for MCP-1; 17.8% ± 20% for %CD16+ monocytes; 18.9% ± 6% for sCD14. Assuming 80% power, alpha=0.05 and using the primary outcome requiring the most subjects for which data are available (MCP-1), we would require a total of 24 subjects (12 in each arm). Allowing 20% loss to follow-up would result in a total study sample of 30 subjects. Secondary measures include monocyte CX3CR1 & TF, plasma TNF, sCD163 & sTF. Treatment effects for primary outcome measures will be analyzed by linear mixed effects models. These models are similar to repeated measures ANOVA, but can handle both the inherent correlation due to multiple observations from the same subject as well as missing observations due to loss to follow-up or other reasons. Repeated measures ANOVA may be used if data are complete and underlying assumptions are met. Non-linear models, such as generalized estimating equations (GEE), will be used if distributional assumptions are not met by the data. Parameters described above are the primary & secondary outcome measures of this study, while the two items described below will be exploratory. Dr. Ratcliffe, study biostatistician, is experienced with all aspects of this type analysis, including the application to various aspects of HIV/AIDS pathogenesis & treatment, SIV, and in HAND.