Effects of Diet on Brain Processing (EDBP)

Study Protocol, Statistical Analysis Plan & Consent Form

NCT02835820

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Shannon Morrison, PhD, Principal Investigator
University of Alabama at Birmingham
Birmingham, AL 35294

STUDY SUMMARY

1. INTRODUCTION

1.1 Background

Poor cognitive function is a serious problem in the aging HIV-positive population. It has been estimated that 52-59% of adults with HIV have cognitive impairment.[1,2] Such cognitive impairments are known to interfere with medication adherence, compliance to medical appointments, emotional well- being, and everyday functioning (i.e., driving and financial management).[3-7] The source of this cognitive impairment appears to stem from both the viral infection as well as from the agents used to treat the disease. For instance, even though HIV replication may be hindered with antiretroviral therapy (HAART), HIV continues to produce neuro-inflammatory proteins (e.g., TAT, gp120); likewise, some HAART medications may produce metabolic and neurotoxic effects that reduce brain reserve (i.e., the brain's ability to cope with impairment while maintaining functionality)[7]. For example, HIV positive individuals prescribed HAART demonstrate reduced *N*-acetylaspartate (NAA) and decreased levels of NAA in persons prescribed HAART are associated with brain mitochondrial toxicity,[8] and reduced brain energy metabolism. Although the cause for cognitive decline commonly observed in the HIV positive population is not entirely clear, it is likely linked to inflammation and/or deficits in available energy. Thus, treatments that address inflammation and brain energy metabolism may prove beneficial for prevention or reversal of cognitive decline in the aging HIV-positive population.

One such treatment is a ketogenic diet (KD) (i.e. < 50 grams of dietary carbohydrate (CHO)/day). In the absence of available CHO, the body burns" fat as a fuel, which creates ketones as a by-product. Ketones are a highly efficient metabolic fuel readily used by the brain.[9] While the precise mechanisms are unclear, KDs have been associated with improved brain fuel metabolism, neural antioxidant effects, reduced expression of crucial genes involved in inflammation, greater adenosine triphosphate (ATP) production, and increased mitochondrial biogenesis in animals[10,11] and humans.[12,13] More importantly, these physiological adaptations have been linked to improved cognitive function in other neurological disorders (i.e., Alzheimer's[13] and Parkinson's disease,[14] *amyotrophic lateral sclerosis* (*ALS*),[15] and epilepsy)[12,16] and have enhanced memory improvement in older adults with pre- existing mild cognitive impairment.[17] While the metabolic and neurologic benefits of a KD are well documented in some populations,[18] the neurocognitive, inflammatory, or cardiometabolic effects of a KD in medically stable older HIV patients have not been explored. *This study will address these gaps*.

2. **1.2 Preclinical Data.** N/A
3. **1.3 Clinical Data to Date**

   To our knowledge, this is the first study to examine the effects of a Ketogenic Diet in an HIV human population. However, animal studies support the potential cognitive benefit of a ketogenic diet in the context of HIV infection.

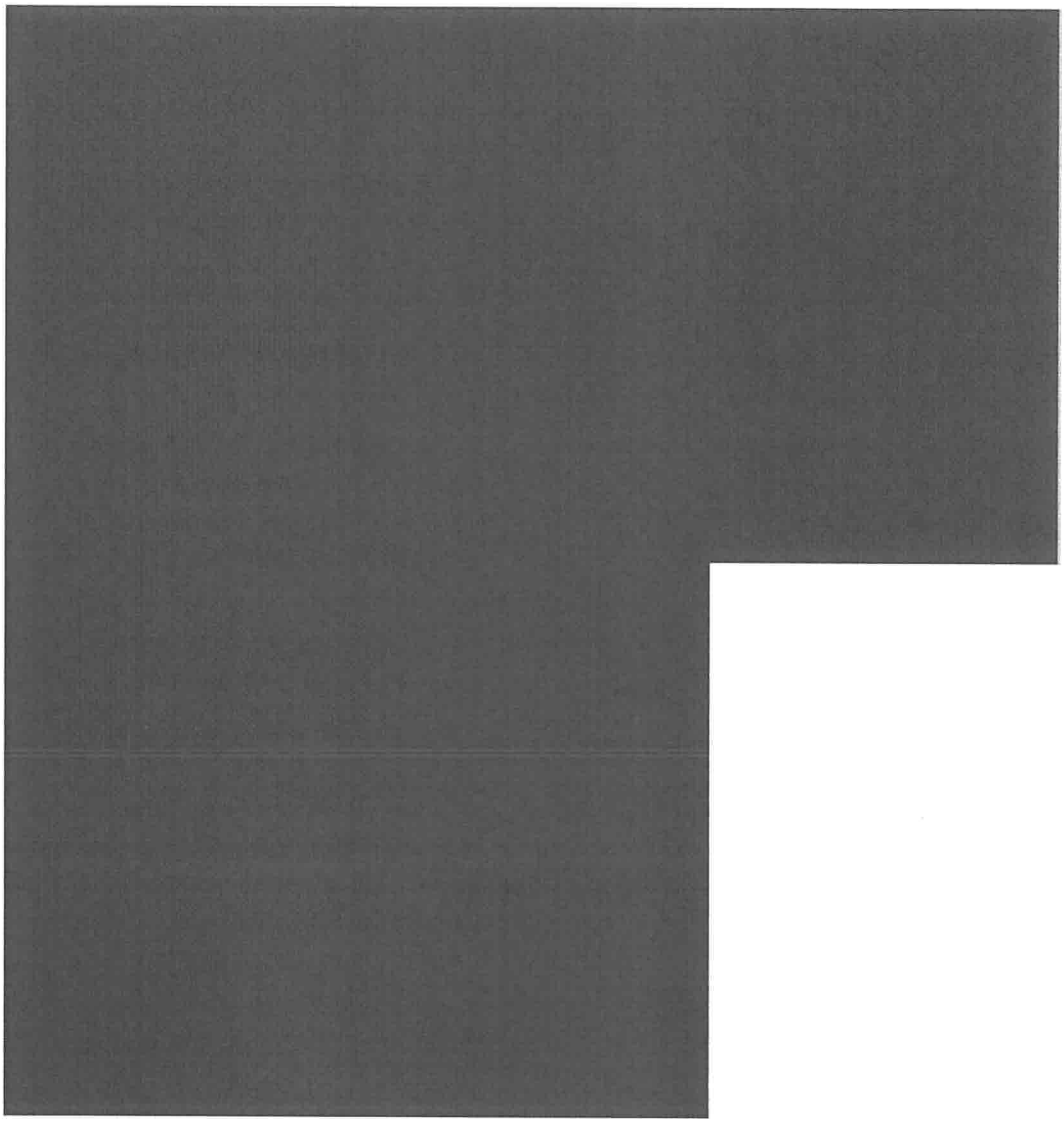
2. STUDY OBJECTIVES

In medically stable, older (> 50 years) HIV patients with cognitive impairment, this study will: Test the feasibility of recruitment, retention, and adherence to a ketogenic diet versus patient choice diet (PCD) intervention.

2.1 Primary: Compare the impact of a 12-week KD versus PCD on:

1. *2.1.1* Cognitive function *(at 12 weeks).*
2. 2.1.2 Inflammation *(at 12 weeks).*
3. 2.1.3 Cardiometabolic profile *(at 12 weeks).*
4. *2.1.4* Persistence of cognitive effects *(at 18 weeks).*

3. STUDY DESIGN: Randomized, 2-group pre/post design. Participants randomized using permutated block randomization using an algorithm developed by the UAB Center for Clinical and Translational Science Biostatistics, Epidemiology, & Research Design (BERD) team. Due to the nature of the intervention (diet) it isn't possible for participants/study personnel to be blinded.
4. SUBJECT SELECTION



4.1

4.2

4.3

INCLUSION CRITERIA .....

> 50 years with stable HIV and cognitive impairment as determined by the Modified Telephone Interview for Cognitive Status (TICS-M) Scale. Participants required to have stable HIV infection as evidenced by CD4+ lymphocyte count > 350 cells/mm^3 for at least two years and prescribed their current cART regimen for at least six months.

EXCLUSION CRITERIA .....

Current drug or alcohol abuse (> 3 drinks/day), past medical history of mental disorders (i.e., schizophrenia, bipolar), neural injury (i.e., cerebral vascular accident or traumatic brain injury), dementia, Parkinson's, diabetes mellitus, hearing impaired, or any other condition that contraindicates participation.

Subject Recruitment and Screening

Participants recruited from the UAB 1917 HIV/AIDS Clinic using fliers within the clinic as well as by advertisement on a rolling kiosk located in the clinic lobby.

5 STUDY PROCEDURES

Following IRB approval and informed consent, eligible participants randomized to either the experimental (n = 7) or control group (n = 7) and scheduled for baseline data collection. Laboratory, demographic, and anthropometric assessments were completed UAB's Clinical Research Unit (CRU). Baseline data: demographic questionnaire, oral glucose tolerance test (OGTT), inflammatory assays and lipid panel as well as an anthropometric evaluation. Even though all snacks and meals for the KD group provided, KD group participants also provided nutritional counseling specific to the KD as well as provided with handouts. Food selected from an 8-day menu. Meals matched for energy content to maintain current energy balance (eucaloric) consisting of < 50 grams CHO/day. Daily CHO intake primarily derived from fresh vegetables.

After laboratory assay and body composition assessments collected, questionnaires and cognitive testing in a private conference room away from outside distractions completed. Delivery of meals/snacks (week 1) to begin the week following baseline data collection.

Food delivery via courier on the same day of the week across the study. All frozen/refrigerated items delivered in a commercial grade cooler. All items clearly labeled with easy-to-understand preparation instructions.

Data Collection

Data collection in the UAB Clinical Research Unit after a 12-hour fast collected by registered nurses well-versed in research methodology. Data collection described below. **Data collection collected at baseline**

and week 12 unless otherwise stated. NOTE: Cognitive assessments completed at baseline, week 12, and week 18.

Demographics (baseline only): Age, education, gender, marital/partner status, employment status/disability eligibility, SES (Medicaid, food stamps, public housing eligibility), years since HIV diagnosis (baseline only).

Anthropometrics: Height, weight, BMI, waist and hip circumference (baseline/wee 12). Height (nearest 0.1 cm), waist circumference (nearest 0.1 cm), and hip circumference (nearest 0.1 cm) measured with Gulick tape measure. Weight (nearest .01 kg) assessed using a Tanita body composition analyzer BC418, Tanita Corp of America, Arlington Heights, IL. BMI calculated.[23] Waist circumference measured at the umbilicus at end of inspiration. Hip measures evaluated at widest hip portion.

Oral Glucose Tolerance Test (OGTT): 75 g at baseline (time 0). At ~7 am, after a 12-h fast, a flexible intravenous catheter will be placed in an antecubital space. Blood samples will be collected at times 0, 10, 20, 30, 60, 90, and 120 minutes. OGTT performed at baseline. Fasting glucose, insulin, and c-peptide to be assessed at week 12.

Lipids: Total, high density cholesterol (HDL) and triglycerides were measured using SIRRUS analyzer and low density lipoprotein were calculated using the method of Friedewald.[30]

Inflammation Markers: Assessed by immunoassay in fasting morning sera before and after the intervention. High-sensitivity C-reactive protein (CRP), TNF-a and IFNy, IL-1B, IL-6, IL-8, and IL-12p70

Cognitive Battery Domain

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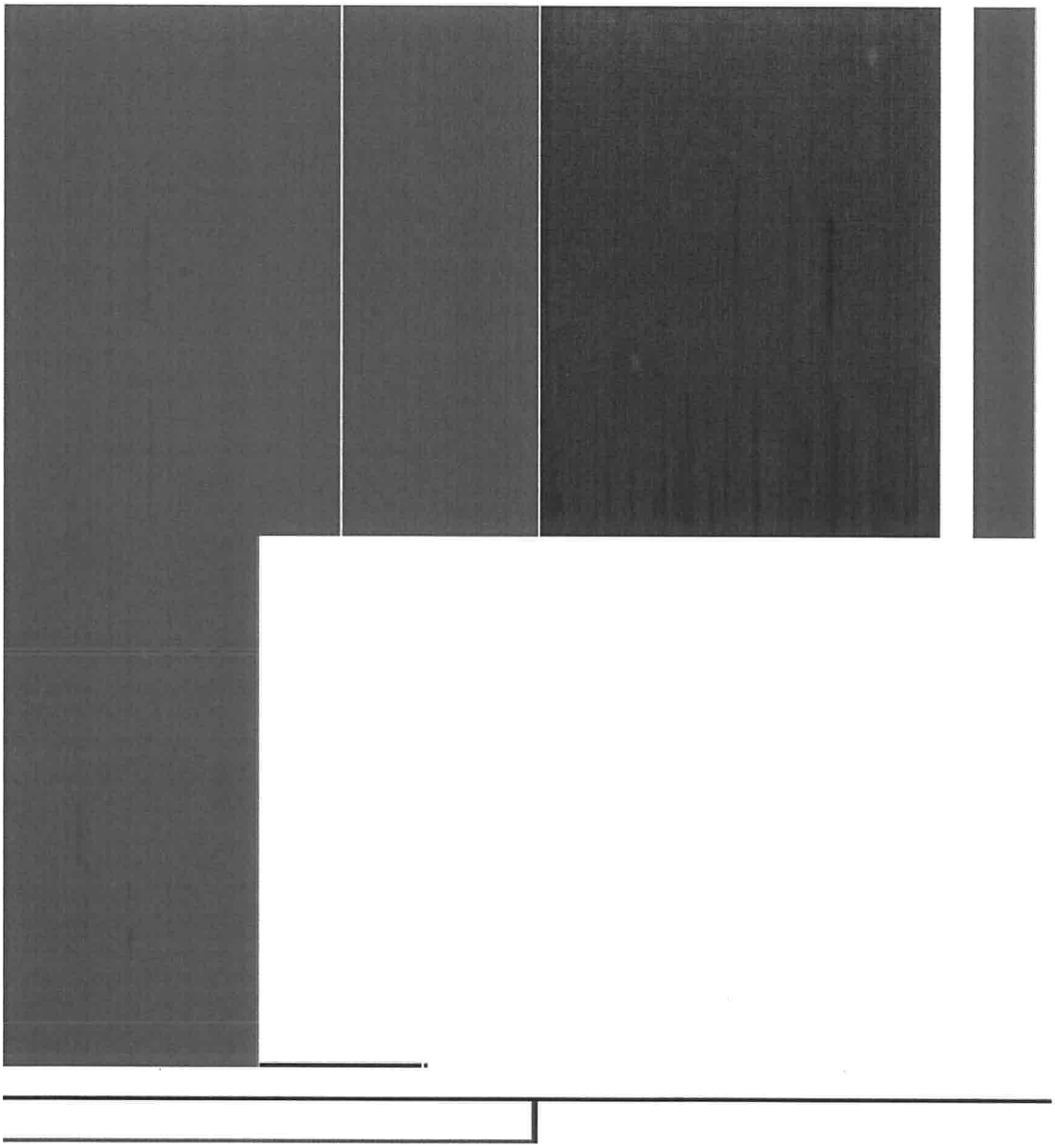


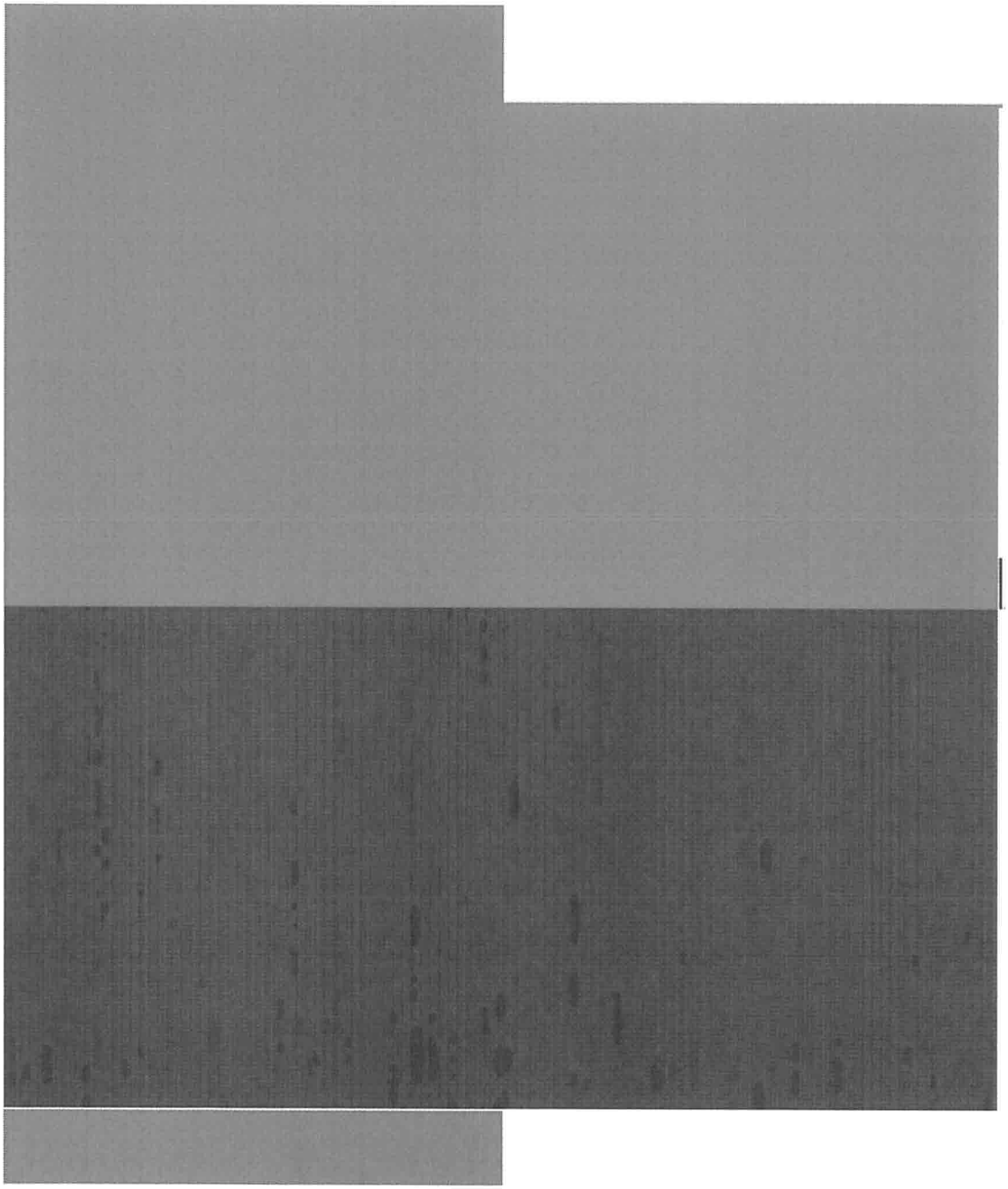
Cognitive Measures

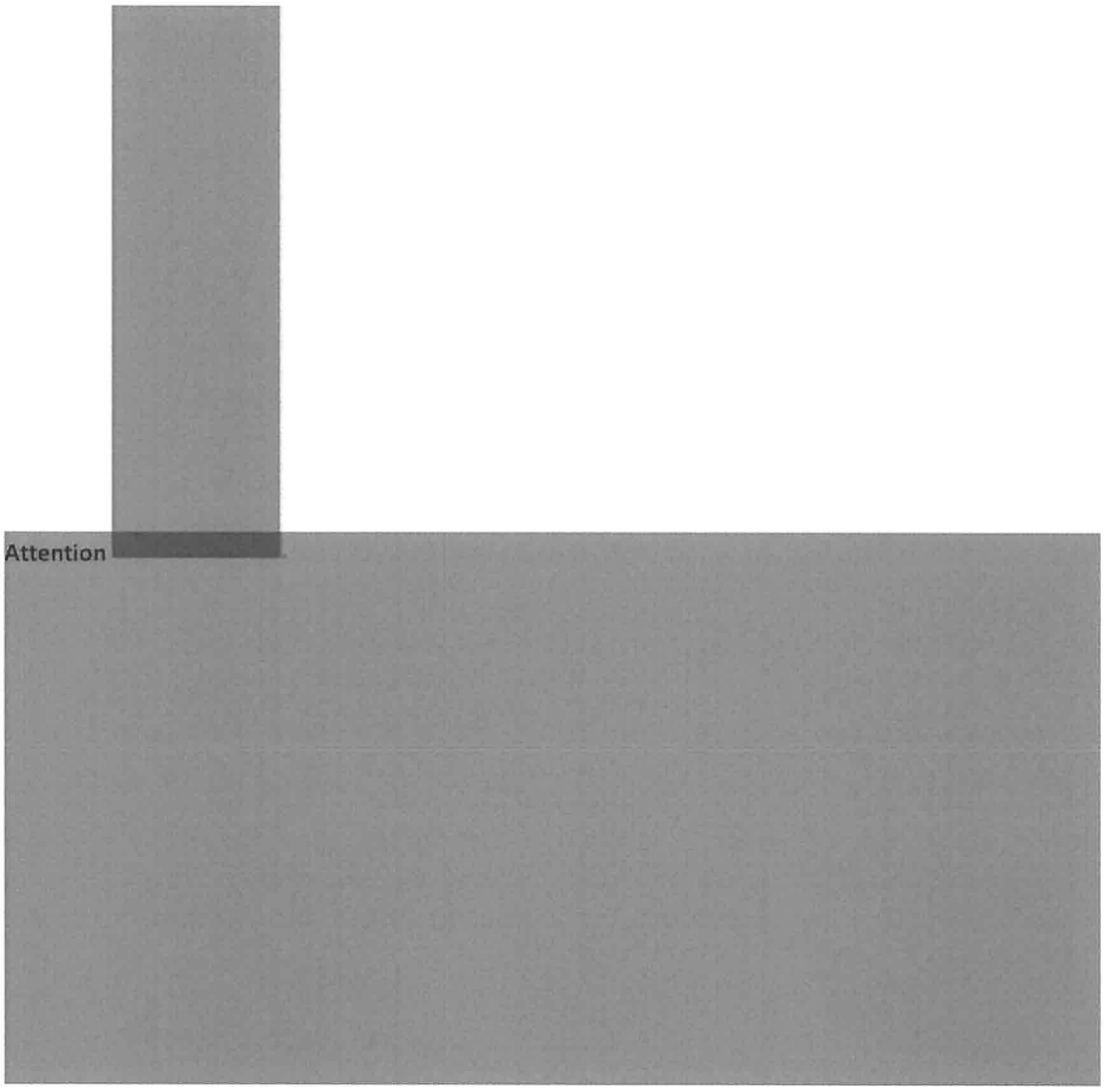
Speed of Processing

WAIS-III Digit Symbol measures visuospatial tracking, attention, and speed of processing. Participants are presented with a key which has numbers paired with a unique symbol. They are given rows of numbers with blank spaces underneath them. The task is to use the key to fill in the blank spaces with the symbol that corresponds to that number. Scores are calculated by the number of squares filled in correctly.

WAIS-III Symbol Search is similar to the Digit Symbol Test. Participants are given rows of symbols and must use the key to write the corresponding number (1-9) in the blank under the symbol.

Trails Making Test A – This measure of motor speed and speed of processing is very reliable (r = 0.80 – 0.90) Twenty-five circles numbered 1 to 25 are located randomly on the page. Participants instructed to connect the dots sequentially (1-2-3-4). The score is determined by the time to complete.

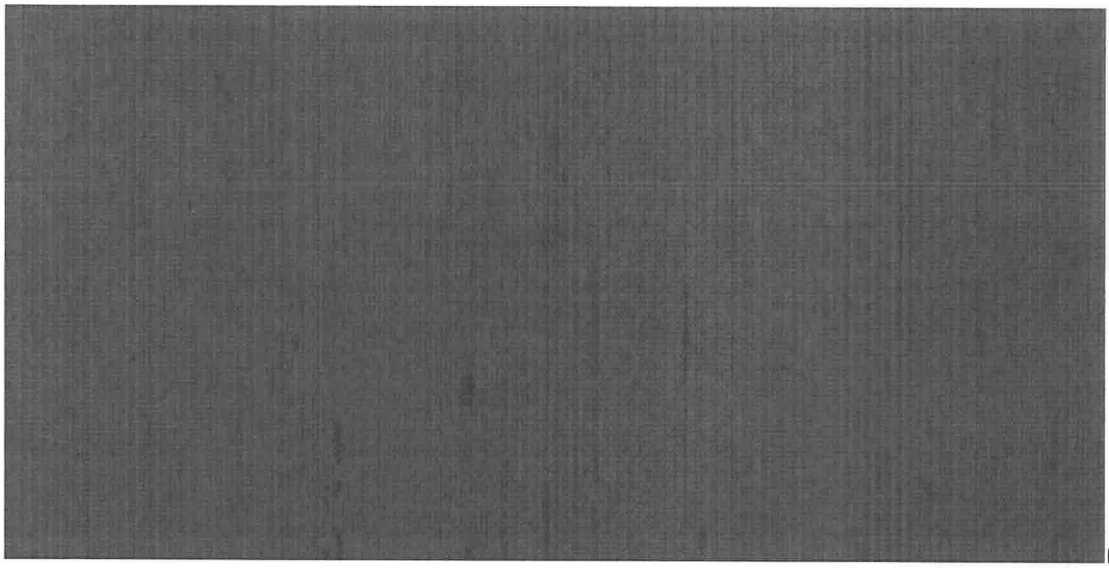




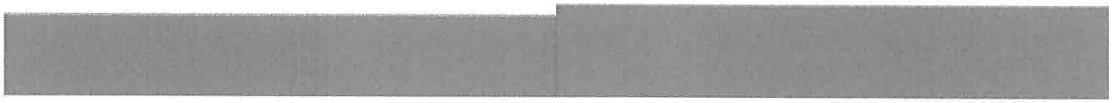
WAIS-III

Digit Span – A measure of attention and concentration. Participants must recall blocks of sequenced numbers (1 through 9) presented to them; the length of the blocks are small at first and slowly build making it more difficult to attend. Digits are to be immediately recalled forward (e.g., 1..2..3) and backward (e.g., 3..2..1).

Verbal



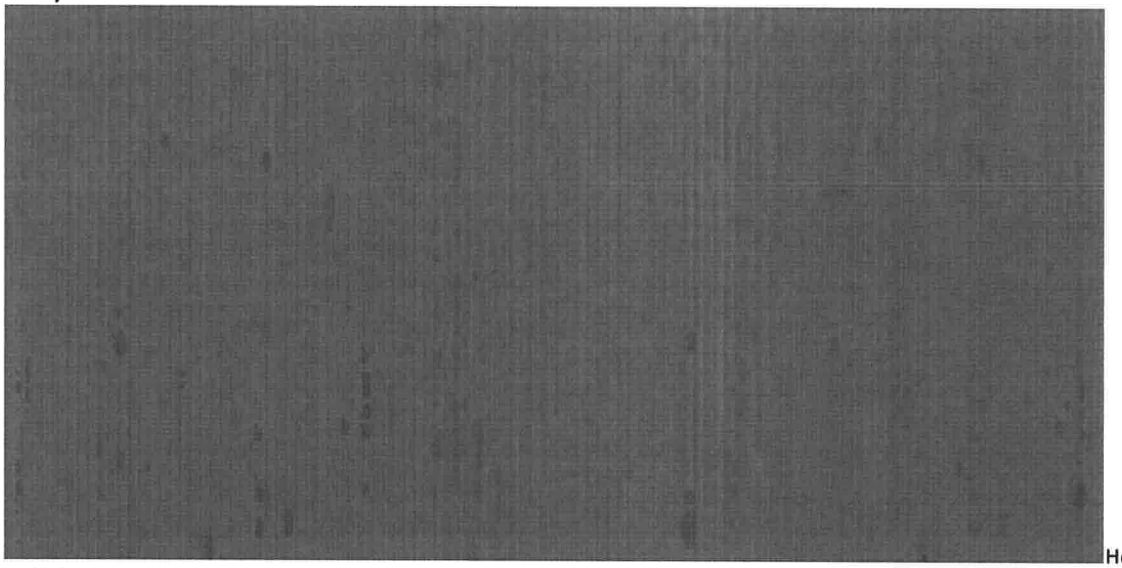
Hopkins Verbal Learning Test-Revised (HVLT-R) Trials 1-3 – A test of verbal recall and consists of 12 words, four



from each of three semantic categories. The total recall is used in analyses, but true-positive recognitions and false-positive errors can be used.

Learning/ Memory

Delayed



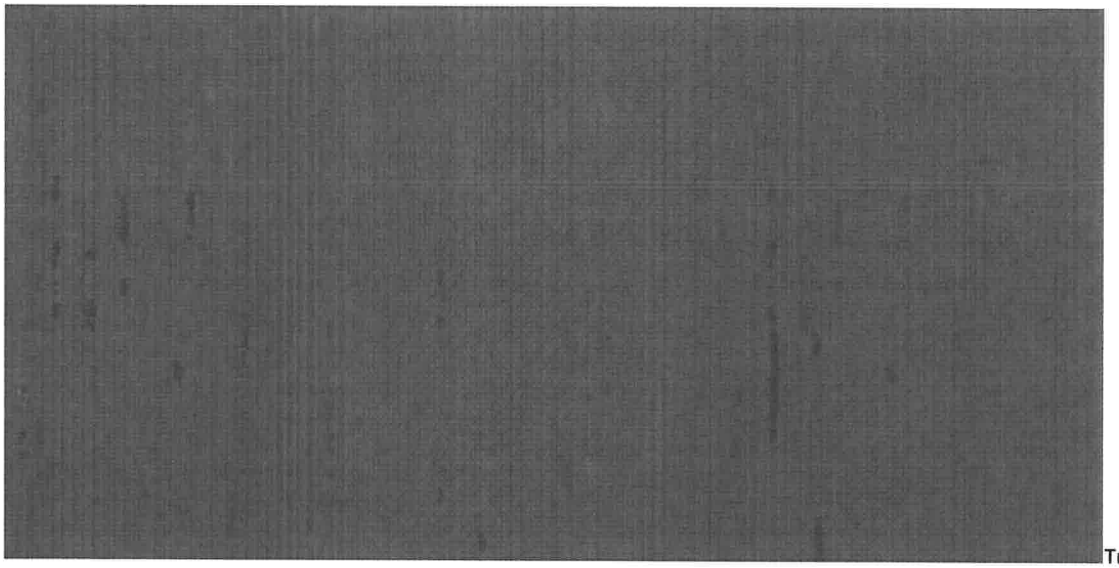
Hopkins

Verbal Learning Test-Revised Delay – A test of delayed verbal memory, it is administered 25 min after the

HVLT-R Trials 1-3 to measure long-term verbal memory. Scores equal the sum of the words correctly recalled.

Verbal
Memory

Executive



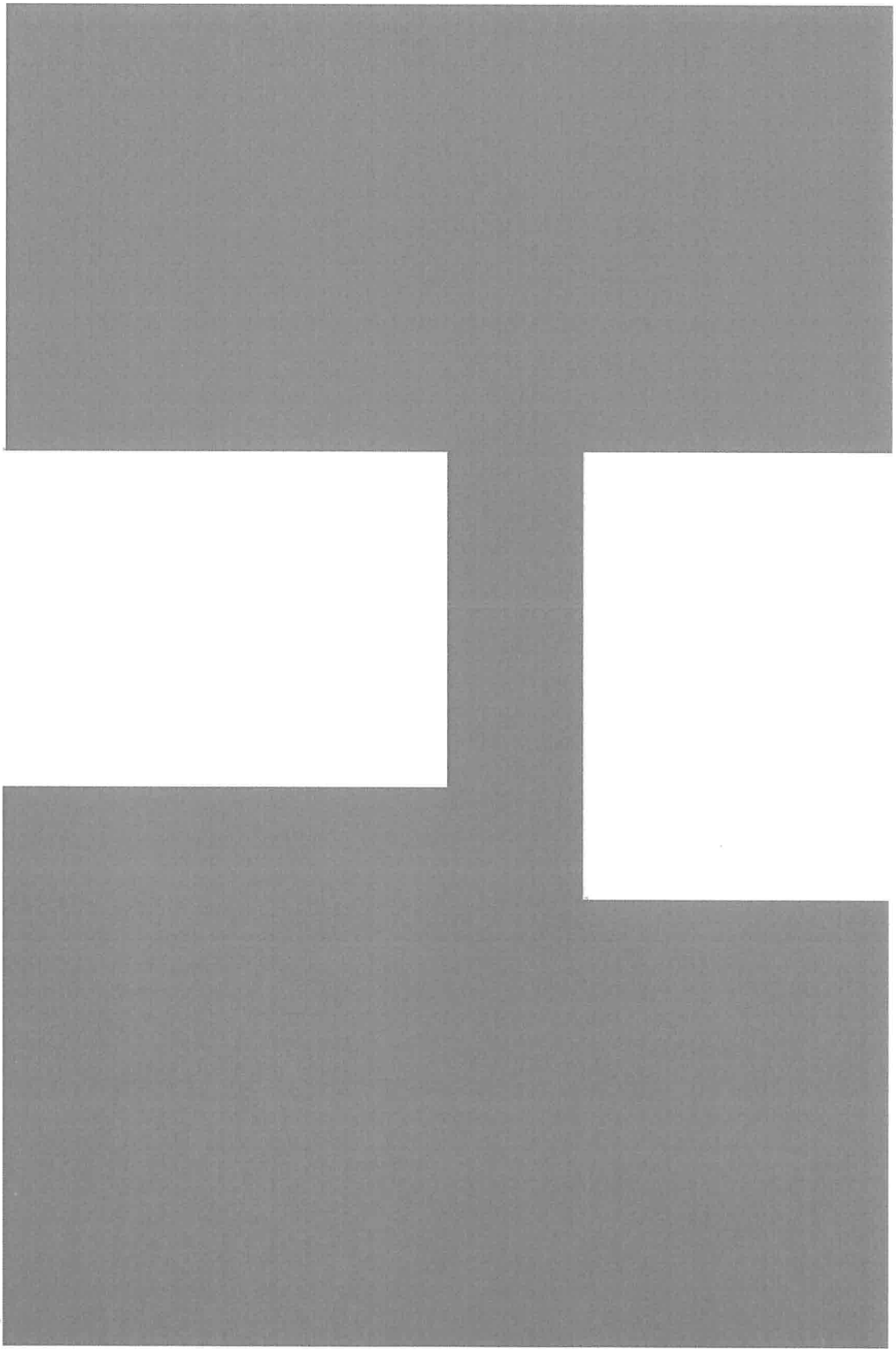
Trails

Making Test B –Participants are scored on the time it takes to connect 25 circles in an ascending pattern that

Function

requires alternation between numbers (1 to 13) and letters (A to L) (i.e., 1-A-2-B-3-C, etc.). Thus, a good performance on this test requires mental alertness and contrentrated attention as well as the ability to shift between numbers and letters (i.e., cognitive flexibility).

Stroop Interference – A measure of selective attention and executive function. Participants are presented with names of colors printed in a conflicting colored ink. First, they will read the printed color name. Second, they will name the color of the ink in which the word is printed. The time to complete each task is recorded. The difference between the times is calculated. The greater the difference between the times for task 1 and 2, the poorer their executive functioning.



6. STATISTICAL PLAN

Sample Size. Feasibility and preliminary data for effect size estimation is the primary purpose of this pilot

study (hypothesis generating).

Descriptive analyses.

Demographic, Anthropometric and Baseline Characteristics: Demographic data (i.e., age, education, gender, marital/partner status, employment status, and years since HIV diagnosis were evaluated using frequencies and reported for each group. Ratio/interval data (i.e., anthropometrics (i.e., height, weight, BMI, waist and hip circumference, cognitive performance by instrument; inflammatory markers (CRP, TNF-a, IFNy, IL-1B, IL-6, IL-8, and IL-12p70); cardiometabolic factors (OGTT, glucose, C-peptide, and insulin) reported via mean/SD at baseline by group. Between-group t-tests will explore group differences at baseline.

Primary analysis: All the primary outcomes (impairment score, inflammatory markers and cardiometabolic factors) will be examined by an analysis of covariance (ANCOVA) including the change from baseline to completion of diet treatment as dependent variable, study group as independent variable, and baseline measures as a covariate, to evaluate the effects of a 12 week KD versus PCD. The lasting cognitive effects of a 12-week KD versus PCD six weeks post intervention completion was determined by an ANCOVA including the change of impairment score form 12 week to 18 week as dependent variable, study group as independent variable, and impairment score at 12 weeks as a covariate.

7 SAFETY AND ADVERSE EVENTS

Loss of confidentiality is unlikely but possible. The breach of confidentiality could result in disclosure of HIV status.

During the OGTT procedure, there is a risk of a bruise, slight pain, inflammation of the vein, bleeding at the site of puncture and fainting. There is also the rare possibility of infection. Only an experienced, registered nurse will draw blood; so the likelihood that these problems will occur is low. The cleansing of the site prior to puncture and the maintenance of sterile techniques will minimize the risk of infection. There will be some discomfort when the tube is placed in the arm. Participants will also be at risk of developing hypoglycemia (low blood sugar) which may cause light headedness, sweating, shakiness, and dizziness. Severe low blood sugar can cause seizures and/or coma. These problems are very rare and we prevent them by

close monitoring of participant's blood sugar level.

Venipuncture for blood draw will be performed 2x (baseline and week 12). There is some risk for bruising or discomfort during venipuncture. Risk of minor bruising is observed at an approximate rate of 12% and larger, more extensive bruising occurred at approximately 3% of all venipunctures. Bruising is anticipated to be minimal and resolve without intervention.

Mild discomfort associated with venipuncture is a normative experience as this requires a small puncture of the skin; however, the discomfort is minimal and very short in duration (< 5 seconds). No long-term effects anticipated as a result of the mild discomfort of venipuncture performed by a licensed registered nurse.

Hypoglycemia incidence during OGTT is approximately 6%. Severity is likely to be minimal as these participants will be monitored by a registered nurse during the entire OGTT. Registered nurses are trained to recognize signs/symptoms of hypoglycemia and to respond appropriately. Effects of hypoglycemia are immediately reversible with administration of oral glucose in a conscious patient. MD consultation is available.

Mild psychological discomfort may occur during completion of cognitive battery and/depression scale; however, the discomfort would be short in duration (30 minutes – 1 hour). Prevalence of test anxiety is believed to be higher in older versus younger adults and may be due to concerns over cognitive decline;

5

6 although prevalence is unknown. Nonetheless, even in those individuals with testing anxiety, the effects are

short in duration. In addition, there are no known lasting testing anxiety effects in older populations.

Diet: Those randomized to the KD may experience normal transient reactions such as hunger, weakness,

lightheadedness, constipation, fatigue, dizziness, or cravings for certain foods during the first few days of the

KD; however, these effects are mild in nature and resolve without intervention as the body adapts to the

new diet. No known long-term risks associated with KD. The most common adverse effects are constipation

(prevalence ~30%), loss of energy (prevalence ~35-37% and bad breath (prevalence ~ 43%), all of which

resolve within few weeks as the body adapts to the new diet. Daily energy intake eucaloric (weight

maintaining) so changes in weight not anticipated.

Inquiry regarding adverse effects assessed by project coordinator at week 4, week 8, and week 12. Study

physician notified immediately for serious adverse effect. In addition, documentation submitted to the IRB

submitted within three business days after any adverse effect reported. Medical monitoring conducted by

primary investigator in collaboration with the study physician. Monitoring completed by registered nurses

during data collection in the Clinical Research Unit.

All testing will be performed by trained personnel, blood samples will be collected by registered nurses, and all equipment will be calibrated daily before testing. Prior to giving consent, all potential participants will be allowed to see equipment and facilities. If an individual indicates discomfort or the desire to discontinue testing, tests will be terminated immediately.

During routine visits and telephone calls, the study coordinator will query participants for any adverse events since their last contact with study personnel. In the case of an adverse event during times of testing, a study physician will be on call. A medical doctor will provide medical supervision for this study. All adverse events will be reported to the UAB IRB and reviewed by the investigative team. Should any of these individuals and/or the IRB identify that any adverse event may be related to the study protocol, testing will be suspended and the protocol will be amended accordingly.

Transient testing fatigue is likely to occur by the end of data collection on weeks 1 and 12; however, the fatigue will be minimized by the provision of a 45-minute break and a meal following the OGGT.

8 DATA HANDLING AND RECORD KEEPING CONFIDENTIALITY

Loss of confidentiality: Participant information kept confidential to the extent allowed by law. However, research information that identifies an individual may be shared with the UAB Institutional Review Board (IRB) and others who are responsible for ensuring compliance with laws and regulations related to research, including people on behalf of the Center for AIDS Research and the Office for Human Research Protections (OHRP). Inform participants that results of the treatment may be published for scientific purposes; however individual identifies will not be disclosed. Participants will be assigned

a study ID number, which will be used for identification of data collected. No personal identifiers on any data beyond the demographic sheet will be included. As such, the demographic sheet is the single study identifier with corresponding participant name. The demographic questionnaire will be secured in a locked cabinet in the PI's locked office until participant data collection complete and data are entered. Data entry into a Redcap database will only occur on a secure computer under direct supervision of the project coordinator or PI. Only study staff approved on the IRB protocol will have access to the database.

Source Documents & Records Retention

A chart will be created for each participant after consent. During study participants, charts will be maintained in the project coordinator's office located in the Center for Clinical and Translational Sciences in

7 a secure cabinet in a locked office. After study completion, charts will be maintained in the PIs locked office

cabinet located in a secure building requiring approved access to enter for seven years.

9 STUDY MONITORING, AUDITING, AND INSPECTING

Recruitment (i.e., screenings and enrollment) will be evaluated quarterly by the PI. Demographic data of screening/enrollment will also be reviewed at that time. The demographics of the patients at the recruitment site reflects national HIV trends. We anticipate our sample to mirror greater minority representation; however, we anticipate few Hispanic participants due to a significantly greater African American population in comparison to Hispanic residing in Birmingham, AL.

AUDITING

The PI will be provided invoices for study expenses that will be forwarded to the financial administrator for research in the Center for Clinical and Translational Sciences for payment. Neither the PI or study staff will have access to project funds.

Recruitment and study progression will also be reviewed by the UAB IRB. Annual progress reports are required to maintain IRB approval.

10. REFERENCES

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CONSENT FORM

TITLE OF RESEARCH:	The Effect of a Ketogenic Diet on HIV-Associated Neurocognitive Impairment
ALTERNATIVE TITLE:	Effect of Diet on Brain Processing (EDBP Study)
IRB PROTOCOL:	F151009003
INVESTIGATOR:	Shannon Morrison, PhD, CRNP, FNP-BC
SPONSOR:	Center for Clinical and Translational Science

Purpose of the Research

We are asking you to take part in a research study. This research study will test whether a particular type of diet helps older HIV+ individuals who have problems with brain processing think and remember better. This study will enroll 20 men and women aged 50 years and older.

Explanation of Procedures

If you decide to enter the study, you will come to UAB for one testing visit at the beginning of study, after 12 weeks, and after 18 weeks. The initial visit time will vary based on what group you are randomly assigned to as well as other factors. For most participants, 5 – 6 hours will be required for the baseline and week 12 visits and 1 hour for the 18-week visit. A small number of participants will also complete an additional neuroimaging test (MRI of the brain) that will take approximately an additional hour to complete during both the baseline data collection and 12-week visits.

If you decide that you want to participate and complete this informed consent, you will be randomly picked (like the flip of a coin) by a computer to receive one of two diets: The ketogenic diet (KD) or the Patient Choice Diet (PCD).

Ketogenic Diet:

The KD is very low in carbohydrate-containing foods. This means that you will be asked not to eat foods with high amounts of sugar or starch, such as bread, pasta, potatoes, rice, sugary drinks, and sugary fruits and desserts. To replace these foods in your diet, you will be asked to eat protein and fat-containing foods such as beef, pork, poultry, fish, eggs, cheeses, avocados, olive oil, and coconut oil. You will also be encouraged to eat a variety of non-starchy vegetables such as salad greens, green beans, kale, and broccoli. You will receive three meals per day delivered to your home for the 12-week study. In addition, you will also receive written samples of the types of foods that you can eat while on your diet to aid your selection in eating outside of your home.

You will be provided with urine ketone sticks to use at home. These sticks reflect how much fat you are burning as a fuel. You will measure ketones at home every day for the first 2 weeks, and then at least once a week. You will measure 3x/day (upon arising and 2-4 hours after lunch and dinner). You will be asked to write down the urine ketone results. In addition, on weeks 4 and 8, you will be asked to photograph the urine ketone stick results and send the pictures to a member of the research team.

A small group of 5 individuals randomized to the KD group will also be asked to undergo a magnetic resonance image (MRI) of their brain at the beginning of the study and after 12 weeks consuming the KD diet. This is to assess how changes in the diet modify blood flow to the brain. The first 5 participants randomly assigned to the KD group and have no medical contraindications related to MRI imaging (such as claustrophobia, pacemaker, or metal pins/screws) will be selected for MRI imaging.

MRI of the Brain: A small number of participants will be asked to participate in MRI scanning of the brain (total 2 MRI scans: baseline and after 12 weeks in the study). If you are a part of the small number of participants invited for the MRI brain scan, you will be escorted to UAB Highlands for the MRI scan after completion of the cognitive testing. To complete the MRI, you will be asked to lie on a long narrow padded table for about 15 – 30 minutes while the MRI scanner gathers information. The space within the magnet in which you lie is somewhat confined; if you feel claustrophobic (an unpleasant feeling of being closed in) you can discontinue the scan at any time. During the scan, you will be exposed to a magnetic field and radiofrequency magnetic fields, but you will not feel either. You will hear repetitive noises; however, and you will wear earplugs to reduce this noise. A sensor will be placed on your left index finger to monitor heart rate as well as a band around your chest to monitor breathing. You will also be given a squeeze ball that activates an alarm if you need to stop the scan at any time. The MRI of the brain will take approximately an extra hour to complete on the first visit as well as the 12-week visit.

If you do not wish to undergo or are unable to complete a MRI of the brain due to medical issues (i.e., claustrophobia, pacemaker), this does not mean that you cannot participate in the study.

Patient Choice Diet:

Participants randomized to the Patient Choice Diet (PCD) will continue to consume their routine diet. There will be no dietary restrictions for those placed on the PCD; however, you will be asked to complete a urine ketone test 3x/day (upon arising and 2-4 hours after lunch and dinner) for the first two weeks and then weekly thereafter. You will write down the result of each test on a log that we will provide to you. In addition, on weeks 4 and 8, you will measure the urine ketones after lunch, photograph the urine ketone stick results, and send the pictures to a member of the research team.

Participants in both diet groups will be asked to come to UAB for study visits at Weeks 1, 12, and 18. The following tests and procedures will be performed either by clinic staff at UAB or by you at home.

Week 1 Visit

You will come to the UAB Clinical Research Unit (see attached instructions). After your arrival, you will complete the informed consent and answer a few questionnaires related to your background (i.e., age, education), mood, and current diet practices. This will take about 20 minutes.

- *Vital signs and body measurements:* We will assess your heart and respiration rates, blood pressure, and temperature. In addition, we will ask you to step on a scale to measure your weight and a tape measure to assess your height as well as the diameter of your hips and waist. (This will take approximately 5-10 minutes)
- *Blood Draw and Oral Glucose Tolerance Test (OGTT):* You will be asked to come after having fasted overnight. A soft and flexible tube (i.e., saline lock: similar to an intravenous needle [iv] but without any IV fluids being administered. will be placed in one arm to draw your blood; so we will stick you with a needle only once. We will use this to collect blood samples (rather than a new stick). We will measure your cholesterol, markers of body inflammation, insulin and glucose (blood sugar) levels. You will then consume a sugary drink, and we will measure your blood sugar levels over 2 hours. This test is designed to determine how your body responds when you consume sugar. We will take approximately 9-10 teaspoons of your blood to complete these laboratory tests. This process will take approximately 2.5 hours to complete.
- *Break:* After the completion of the blood draws, you will be provided a meal and a 45 minute break to eat and rest.
- *Nutrition education*: If you are assigned to the "Ketogenic Diet" group, after the break you will meet with a dietitian to review some basic information about the diet plan and review meal delivery (approximately 30 minutes). In addition, instructions on how to complete, record, and report the urine ketone results during the study will be reviewed. In addition, urine ketone instruction information and a log sheet will also be reviewed and provided for you to use as a reference at home.
- *Cognitive Testing:* You will be administered several cognitive and everyday functioning measures that will determine how will you can remember, reason, think, quickly, and perform everyday activities such as counting change. These will take about 30 minutes to an hour to complete.
- *MRI of the Brain*

The Week 1 visit will take approximately 5-6 hours of your time. If you are chosen for the MRI subgroup, you should expect the visit to take another hour to complete.

Activities to be completed at home weeks 1-12

Weeks 1 -3 (home)
You will check your urine ketones in the morning, noon, and evening and write down the results on the log sheet provided. You will be provided written and verbal instructions on how to collect the sample and interpret the results.

Week 4 (home)

- Urine Ketone testing (3 times a day/1 day a week) and write down the results on the provided log.
- In addition, send picture of ketone results to research staff after lunch screen

Weeks 5-7 (home)

- *Wednesdays only:* Urine Ketone testing and write down the results on the log sheet provided.

Week 8 (home)

- Urine Ketone testing (3 times a day/1 day a week)
- Send picture of ketone results to research staff after lunch screen

Weeks 9-12 (home)

- *Wednesdays only:* Urine Ketone testing and write down the results on the log sheet provided.

Week 12

(Repeat of tests completed at week 1).

You will come to the UAB Clinical Research Unit (see attached instructions). After your arrival, you will complete the informed consent and answer a few questionnaires related to your background (i.e., age, education), mood, and current diet practices. This will take about 20 minutes.

- Diet and depression questionnaires
- *Vital signs and body measurements*
- *Blood Draw and OGTT*
- *Break*
- *Cognitive Testing*
- *MRI of the Brain*

The Week 12 visit will take approximately 5-6 hours of your time. If you are chosen for the MRI subgroup, you should expect the visit to take another hour to complete.

Week 18 Visit

- *Questionnaires and Cognitive Testing*
- *Exit Feasibility Survey*: Lastly, you will be asked to complete a short questionnaire telling us what aspects of the study that you enjoyed the most and what suggestions you may have for improvement if the study is repeated at a later time. The exit survey will take approximately 10 minutes to complete.

The table below summarizes the study procedures at each visit.

Clinic Visit	Procedures	Time it will take
Week 1	1. Arrive at Clinical Research Unit (CRU) (see attached directions) 2. Completion of informed consent, basic demographic information such as your age, race, and gender as well as a questionnaire to assess information regarding your mood/depression, general health and current eating practices. 3. You will then be escorted by research staff to the Clinical Research Unit (CRU) 4. When you arrive, you will be asked to change into a gown so that your vital signs can be obtained and your height, weight can be measured as well as your waist and hip circumferences measured. 5. You will then have an IV catheter placed in the bend of one of your arms for blood draws. 6. After the IV is secure, a baseline blood sample will be obtained from the (IV). 7. Ten minutes after first blood draw, you be given a sugary drink than you should consume within 5 minutes. 8. After you complete the sugary drink, blood will be redrawn from your IV catheter at 10, 20, 30, 60, 90, and 120 minutes. 9. When this testing is complete, you will be provided a meal and a 45 minute break. 10. Following your break, you will complete some computer tests that measure how well your brain thinks and remembers. 11. Finally, you will meet with a dietician to discuss some basic nutrition information, instructions for urine collection and sending results ect.	**ESTIMATED TIME** If you are not undergoing a brain MRI, then your anticipated time for the week 1 visit one is 5-6 hours. If you are undergoing a brain MRI, then your anticipated time required for week 1 visit is 6-7 hours.

	12. If you are part of the small sample you is undergoing a brain MRI, you will then be escorted to UAB Highlands. After the MRI of the brain is finished, you will be returned to UAB Hospital near the 6th Ave Parking Deck. Completion of the MRI will require approximately one additional hour of your time to complete.	
Weeks 1-3	Urine Ketone Testing (3x/day) morning, noon and evening for 3 weeks. *This just means that you will use a urine dipstick (provided) to test for ketones in your urine and write down the results on a log sheet (also provided)*	
Week 4	Beginning on week 4, you will only need to document urine ketones three times/day on ***Wednesdays.*** On week 4, you will send a picture of the urine ketone results from your noon urine assessment to research staff (Instructions will be provided). Ketone testing instructions - You will be given instructions verbally and to take home with you on how to test your urine as well as instructions on the photograph you will need to send to the research team. Study staff will contact you by email and phone before each time you need to send the picture results of the ketone test at home.	
Weeks 5-7	*Wednesdays only:* Assess urine ketones at morning, noon, and evening and log results	
Week 8	On week 8, you will again send a picture of the urine ketone results from your noon Wednesday urine assessment to research staff (Instructions will be provided).	
Weeks 9-12	Wednesdays only: Assess urine ketones morning, noon, and evening and log results	
Week 12	1. Arrive at CRU. 2. Complete a brief questionnaire. 3. You will then be escorted by research staff to the Clinical Research Unit (CRU) 4. When you arrive at the CRU, you will be asked to change into a gown so that your vital signs can be obtained and your height, weight can be obtained as well as your waist and hip circumferences measured.	**ESTIMATED TIME** If you are not undergoing a brain MRI, then your anticipated time for the week 1 visit one is 5-6 hours.

	5. You will then have an IV catheter placed in the bend of one of your arms for blood draws. 6. After the IV is secure, a baseline blood sample will be obtained from the IV catheter and a second blood draw will be collected 5 minutes later. 7. Ten minutes after first blood draw, you be given a sugary drink that you should drink within 5 minutes. 8. After you complete the sugary drink, blood will be redrawn from your IV catheter at 10, 20, 30, 60, 90, and 120 minutes. 9. When this testing is complete, you will be provided a meal and a break (total approximately 45 minutes). 10. You will complete a few more computer tests that measure how well your brain thinks and remembers. 11. If you are part of the small sample you is undergoing a brain MRI, you will then be escorted to UAB Highlands. After the MRI of the brain is finished, you will be returned to UAB Hospital near the 6th Ave Parking Deck. Completion of the MRI will require approximately one additional hour of your time to complete.	If you are undergoing a brain MRI, then your anticipated time required for week 1 visit is 6 – 7 hours.
Week 18	Arrive to the CRU 1. Complete the computer assessments measuring your brain's ability to think and remember 2. Feasibility exit interview (Tell us what you did and did not like about participating in this study)	**ESTIMATED TIME** ~ 30 minutes – 1 hour 10 minutes

Incidental Findings

We are performing a MRI of the brain for a small number of participants. The MRI of the brain will be used solely for the research purposes described above. It is not a clinical scan intended for diagnostic or therapeutic purposes. Under no circumstance will the investigator, research staff, or imaging staff interpret the MRI scan as normal or abnormal. They are unable to make any medical comments about your scan. The MRI scan will not be looked at or read for any healthcare treatment or diagnostic purpose. If you want your MRI scan to be reviewed by a physician so that the physician can look for medical issues, you can request a copy of your scan, at no charge.

Risks and Discomforts

Randomization: You will be assigned to a treatment group by chance, and the treatment you receive may prove to be less effective or have more side effects than the other study treatment.

Laboratory testing: Taking blood from the arm vein may cause some minor pain at the site of the needle puncture, some bruising occasionally, and rarely fainting. Only an experienced, registered nurse will draw your blood, so the likelihood that these problems will occur is low. The cleansing of the site prior to puncture and the maintenance of sterile techniques will minimize the risk of infection. There will be some discomfort when the tube is placed in your arm.

Diet: There are no foreseeable risks to participating in this study beyond those involved in changing your diet. That is, just as with any diet, if you are randomized to the KD diet, you may experience normal transient reactions such as hunger, weakness, lightheadedness, constipation, fatigue, dizziness, and cravings for certain foods. These reactions should be temporary as your body adjusts to the new diet. In some cases, people on the KD experience and increase in urination and the loss of electrolytes. This side effect can be eliminated by mildly increasing salt intake. There may also be risks that are unknown at this time. You will be given more information if other risks are found.

Depression: During the baseline and posttest assessments of the study, we will ask about your feelings and mood; during which, you may report depression or suicidal thoughts. In such an event, you will be provided referral information for social support or medical services and information on depression. After a week, you will be contacted by a member of the research team to determine whether you met with a social service or medical provider.

MRI: Magnetic fields do not cause harmful effects at the levels used in the MRI scanner. However, it does use a very strong magnet that will attract some metals and affect some electronic devices. If you have a cardiac pacemaker or any other biomedical device in or on your body, it is very important that you tell the operator/investigator immediately. As metallic objects may experience strong attraction to the magnet, it is also very important that you notify the operator of any metal objects (especially surgical clips), devices, or implants that are in or on your body before entering the magnet room. All such objects must be removed (if possible) before entering the magnet room. In some cases, having those devices means you should not have an MRI scan performed. In addition, watches and credit cards should also be removed as these could be damaged. You will be provided a way to secure these items. If you have any history of head or eye injury involving metal fragments, if you have ever worked in a metal shop, or if you could be pregnant, you should notify the operator/investigator. There is also a possibility that you will experience a localized twitching sensation due to the magnetic field changes during the scan. This is expected and should not be painful.

Dizziness or nausea may occur if you move your head rapidly within the magnet. **If you feel discomfort at any time, notify the operator and you can discontinue the exam at any time.**

Testing Fatigue and Discomfort: You may become fatigued or bored during the 4-6 hour testing (depending on whether you undergo MRI scan) sessions. If so, you may request a break. Please ask and one will be provided for you. Also, a 30 minute break and snack is automatically built into your testing visit. In addition, we also ask you to perform mental/cognitive tests that you may find difficult, uncomfortable, or embarrassing; however, these tests are designed to measure your peak mental abilities. For many individuals as they want to do their best, it is normal to feel anxious or worried about not doing well on such tests. We just ask that you do your best; but please keep in mind that no one scores perfectly on these tests.

You will always be welcome to discuss any side effects or issues with any of our study team members. If you experience any side effects from a change in your diet, you may discuss this with our study staff and/or physicians and, if necessary, be further evaluated. However, we do not anticipate any harmful side effects.

Personal Information: Finally, your personal information will be stored in a secure location to prevent access by unauthorized personnel. Only study staff will have access to the information you provide.

Benefits

You may not benefit directly from taking part in this study. This study may help us better understand how this particular type of diet may influence brain thinking and remembering in individuals with HIV who feel that they are forgetful or have trouble remembering.

Alternatives

The alternative to participating in this research is to not participate.

Confidentiality

Information obtained about you for this study will be kept confidential to the extent allowed by law. However, research information that identifies you may be shared with the UAB Institutional Review Board (IRB) and others who are responsible for ensuring compliance with laws and regulations related to research, including people on behalf of the Center for AIDS Research, Nutrition and Obesity Research Center and the Office for Human Research Protections (OHRP). The information from the research may be published for scientific purposes; however, your identity will not be given out.

Voluntary Participation and Withdrawal

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed. You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with this institution.

You may be removed from the study without your consent if the study doctor decides it is not in the best interest of your health, or if you are not following the study rules.

If you are a UAB student or employee, taking part in this research is not a part of your UAB class work or duties. You can refuse to enroll, or withdraw after enrolling at any time before the study is over, with no effect on your class standing, grades, or job at UAB. You will not be offered or receive any special consideration if you take part in this research.

Cost of Participation

There will be no cost to you for taking part in this study. All assessments a related to this study will be provided to you at no cost during the study period. In addition, if you are randomized to the KD group, you will receive the specialty meals delivered to your home during the 12-week study. Those randomized to the PCD will not receive food but will continue to consume the diet of their choice.

Payment for Participation in Research

You will be paid $50 for the completion of the first set of tests and assessments and an additional $50 at week 12 after completion of the same tests and assessments that were performed at the beginning of the study. You will receive an additional $10 at weeks 4 and 8 for returning a picture of the noon urine ketone tests results. At week 18, you will be paid $25 for completion of the cognitive tests. Total payment for completion of the study is $145.00.

You may also be invited to complete MRI testing at the beginning of the study and when you return at week 12. Each participant who completes MRI testing will receive $50 for each MRI test. This means that participants who complete the two MRI scans will receive an additional $100. Total payment for participants who complete all study tests and assessments and the two MRI scans is $245.00.

How you will be paid: At the end of each visit, we will enter your information in the UAB system so that you will receive your payment by mail approximately 2-3 weeks later. Ask the study staff about the method. In addition, **please notify staff if there is an alternative mailing address that you prefer your check to be mailed.**

Payment for Research-Related Injuries

UAB and the Center for Clinical and Translational Science have not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

Significant New Findings

You will be told by study staff if new information becomes available that might affect your choice to stay in the study.

Questions

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, you may contact Clinical Research Support Staff (Mary Love) at 205-975-2758 or Dr. Shannon Morrison at 205-996-7841.
If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

Legal Rights

You are not waiving any of your legal rights by signing this informed consent document.

Signatures

Your signature below indicates that you have read (or been read) the information provided above and agree to participate in this study. You will receive a copy of this unsigned consent form.

Signature of Participant Date

Signature of Principal Investigator or Other Person Obtaining Consent Date

Signature of Witness Date

University of Alabama at Birmingham

AUTHORIZATION FOR USE/DISCLOSURE OF PROTECTED HEALTH INFORMATION (PHI) FOR RESEARCH

Participant Name: _____
Research Protocol: Effect of Diet on Brain Processing or the EDBP Study).

UAB IRB Protocol Number: F151009003
Principal Investigator: Shannon Morrison
Sponsor: Center for Clinical and Translational Research

What is the purpose of this form? You are being asked to sign this form so that UAB may use and release your protected health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your protected health information may be used for the research.

Why do the researchers want my protected health information? The researchers want to use your protected health information as part of the research protocol listed above and as described to you in the informed consent.

What protected health information do the researchers want to use? All medical information, including but not limited to information and/or records of any diagnosis or treatment of disease or condition, which may include sexually transmitted diseases (e.g., HIV, etc.) or communicable diseases, drug/alcohol dependency, etc.; all personal identifiers, including but not limited to your name, social security number, medical record number, date of birth, dates of service, etc.; any past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind, including but not limited to drug/alcohol treatment, psychiatric/psychological treatment; financial/billing information, including but not limited to copies of your medical bills, and any other information related to or collected for use in the research protocol, regardless of whether the information was collected for research or non-research (e.g., treatment) purposes.

Who will disclose, use and/or receive my protected health information? All Individuals/entities listed in the informed consent documents, including but not limited to, the physicians, nurses and staff and others performing services related to the research (whether at UAB or elsewhere); other operating units of UAB, HSF, UAB Highlands, Children's of Alabama, Eye Foundation Hospital, and the Jefferson County Department of Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees and agents, including any CRO; and any outside regulatory agencies, such as the Food and Drug Administration, providing oversight or performing other legal and/or regulatory functions for which access to participant information is required.

How will my protected health information be protected once it is given to others? Your protected health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

How long will this Authorization last? Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

Can I cancel this Authorization? You may cancel this Authorization at any time by notifying the Principal Investigator, in writing, referencing the research protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the protected health information that was provided before you cancelled your authorization.

Can I see my protected health information? You have a right to request to see your protected health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: _____ Date: _____

or participant's legally authorized representative: _____ Date: _____

Printed Name of participant's representative: _____

Relationship to the participant: _____