IMPAACT 2002

(DAIDS Document ID 12051)

Combined Cognitive Behavioral Therapy and a Medication Management Algorithm for Treatment of Depression among Youth Living with HIV in the United States

A Multi-center International Trial of the
International Maternal Pediatric Adolescent AIDS
Clinical Trials Group (IMPAACT)

This file contains the current IMPAACT 2002 protocol, which is comprised of the following documents, presented in reverse chronological order:

- **Letter of Amendment #1, dated 27 April 2018**
- **Clarification Memorandum #2, dated 4 October 2017**
- **Clarification Memorandum #1, dated 6 March 2017**
- **Protocol Version 1.0, dated 19 August 2016**

Letter of Amendment #1 for:

IMPAACT 2002
Combined Cognitive Behavioral Therapy and a Medication Management Algorithm for Treatment of Depression among Youth Living with HIV in the United States

Version 1.0, dated 19 August 2016
DAIDS Study ID #12051

Letter of Amendment Date: 27 April 2018

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) affects the IMPAACT 2002 study and must be submitted to site Institutional Review Boards (IRBs) as soon as possible for their review and approval. Approval must also be obtained from site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB and regulatory entity requirements must be followed.

Upon obtaining IRB approval and any other applicable regulatory entity approvals, each site should immediately begin implementing this LoA.

Sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA

Please file this LoA, all associated IRB and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT 2002. If the IMPAACT 2002 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

IMPAACT 2002

Combined Cognitive Behavioral Therapy and a Medication Management Algorithm for Treatment of Depression among Youth Living with HIV in the United States
Version 1.0, dated 19 August 2016

DAIDS Study ID #12051

Version 1.0, Letter of Amendment #1
dated 27 April 2018

LETTER OF AMENDMENT SIGNATURE PAGE

I will conduct this study in accordance with the current version of this protocol, including this Letter of Amendment, and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (U.S.) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., U.S. National Institutes of Health, Division of AIDS) and institutional policies.

_____ _____

Signature of Investigator of Record Date

_____

Name of Investigator of Record
(printed)

Summary of Modifications and Rationale

The purpose of this LoA is to:

1. Modify the procedures for the screening and enrollment process in addition to the clarifications applied to protocol Section 4.4 in Clarification Memoranda (CM) #1 and #2 to remove barriers to recruitment and allow for more timely enrollment. The requirement that sites approach participants in a randomly assigned order is removed; potentially eligible participants may be approached for screening, as available.
2. Provide other minor administrative updates.

Implementation

The modifications included in this Letter of Amendment are listed below by modification and will be incorporated into the next protocol amendment as specified below. Additions to the text are indicated in **bold**; deletions are indicated by ~~strikethrough~~.

1. Screening and Enrollment Process

Section 4.4, Recruitment, Screening, and Enrollment Process

As noted in Sections 3.0 and 9.1, selection bias is a concern. The protocol includes design features to minimize selection bias, ~~including requiring sites to obtain screening numbers for all potentially eligible participants and randomizing the order in which the site will approach potential participants for enrollment;~~ and collect~~sing~~ limited data on patients who do not enroll so that their characteristics can be compared to those of participants who did enroll (to assess the potential extent of selection bias). ~~New randomized lists will be created for sites as needed.~~

It is expected that site staff will approach all potentially eligible youth for possible study participation. Patients will be recruited, and proceed with the screening process as follows:

1. Sites ~~create a list of all potentially eligible youth at their site and~~ complete a Screening Log in the Subject Enrollment System (SES) for each patient **who is potentially eligible for the study**. ~~from their list~~. Completion of the Screening Log will generate a screening number.
2. ~~Prior to site initiation of formal screening and enrollment into the study, the Statistical Data Management Center (SDMC) will retrieve the lists of potential participants entered, and randomly order all of the screening numbers within each site into blocks. The DMC randomization department will load these blocks into the randomization system and send the blocks to the sites; the team will then notify sites that this process has been completed and that they can begin screening and enrollment.~~
2. Sites may approach **any patient in care at the study site whom they consider to be potentially eligible for the study and who has a screening number.** ~~anyone from their first block of screening numbers. Patients from the subsequent blocks may not be approached until all patients from the previous block are enrolled or have been approached but will not enroll into the study (for any reason).~~ If a patient is interested in the study, they will undergo the informed assent/consent process and be assigned a PID.
3. Sites will submit a "Screening Failure and Non-Enrollment Results Form" using the screening number in the following circumstances: 1) If a potential participant is approached but not interested in enrolling in the study, in this case, only the fact that the participant does not want to consent to the study will be recorded; 2) If a potential participant is approached and is interested

in being in the study, but fails the eligibility criteria **or does not enroll for another reason**; in this case, the form will collect the reason(s) for not enrolling (i.e., ineligibility and associated reasons for ineligibility), in addition to the patient's gender, race, ethnicity age, viral suppression status, depression severity estimate, and mode of transmission. This record will not include other patient-identifying data.

4. When a participant is enrolled into IMPAACT 2002, the screening number, in addition to the eligibility criteria, will be entered into the data base. The DMC randomization system will verify that the screening number is on the list. Enrollment will occur upon successful entry of required eligibility data into the SES. Successful entry into the SES will generate a study identification number (SID).
5. Once enrolled, if a participant is no longer able to participate in the study, an off-study form will be completed.

Ideally, screening and enrollment into the study will be conducted on one day, if the participant is willing and found to be eligible.

Ineligible participants may rescreen for study participation provided their initial reason for ineligibility has changed **or is thought by site staff to have changed**. ~~In addition, those participants listed on the pre-screening list~~ **Participants** who do not screen for the study or do not enroll for any reason may be subsequently assigned new screening numbers, and new potential participants will be assigned screening numbers as they are identified. ~~The SDMC will regularly retrieve the lists of potential participants and steps 2 through 5 above will be repeated as needed to achieve the target study enrollment.~~ **Steps 1 through 5 above will be repeated as needed to achieve the target study enrollment.**

Section 9.1, General Design Issues, fourth paragraph

In addition, the protocol includes ~~several~~ design features to minimize selection bias, including defining eligibility criteria that apply equally to both study arms; requiring sites to obtain screening numbers for all potentially eligible participants~~ and randomizing the order in which the site can approach potential participants for enrollment;~~ and collecting limited data on patients who do not enroll so that their characteristics can be compared to those of participants who did enroll, to assess the potential extent of selection bias.

2. *Updates to the Protocol Team and Site Roster.*

Protocol Vice-Chairs
~~Patricia Emmanuel, MD Lewis A. Barness Endowed Chair Professor and Chair of Pediatrics USF Health; Morsani College of Medicine 2 Tampa General Circle, 5th Floor, Rm 5016 Tampa, FL 33606 Phone: (813) 259-8867 Email: pemmanue@health.usf.edu~~

NIAID Medical Officers
Adeola Adeyeye MD, MPA, **CCFP, LCDR, U.S. Public Health Service Medical Officer, Clinical Prevention Research Branch,**
Prevention Science Program, DAIDS,
NIAID, NIH
Room 8B36 MSC 9831, 5601 Fishers Lane
Rockville, MD 20852-9831
Phone: (240) 669-5005
~~BB: (240) 421-8446~~
Email: ~~adeola.adeyeye@nih.gov~~
Cell: (240) 619-9365
Email: adeyeyeao@niaid.nih.gov

Protocol Data Managers
Korianne Sulzbach, MPH
Frontier Science and Technology Research Foundation, Inc
4033 Maple Road
Amherst, NY 14226-1056

Phone: 716-834-0900 x7219
Email: sulzbach@fstrf.org

Study Site Roster
Site 5055, Children's Diagnostic and Treatment Center
~~Ana Puga,~~
~~CFAP Medical Director~~
~~Children's Diagnostic & Treatment Center~~
~~1401 S Federal Highway~~
~~Fort Lauderdale, Florida 33316~~
~~Phone: 954-728-1017~~
~~Email: apuga@browardhealth.org~~

Kathleen Graham, PharmD
Study Coordinator
Children's Diagnostic & Treatment Center
1401 S Federal Highway
Fort Lauderdale, Florida 33316
Phone: 954-728-1111
Email: kgraham@browardhealth.org

Lisa-Gaye Robinson, MD, MPH
IoR
Children's Diagnostic & Treatment Center
1401 S Federal Highway
Fort Lauderdale, Florida 33316
Phone: (954)728-1136
Email: lerobinson@browardhealth.org

Site 5030, Emory University School of Medicine
~~Bridget Wynn, MPH~~
~~Study Coordinator~~
~~Family & Youth Clinic at Ponce, Room 201~~
~~341 Ponce de Leon Avenue NE~~
~~Atlanta, GA 30308~~
~~Phone: (404) 966-1487~~
~~Email: Bridget.wynn@emory.edu~~

LaTeshia Seaton, MS, APRN, CCRC
Senior Research Nurse
Study Coordinator
Children's Healthcare of Atlanta
Grady-Family and Youth Clinic at Ponce
341 Ponce de Leon Avenue, Room 201
Atlanta, GA 30308
Phone: 404-616-5936
Email: lseaton@emory.edu

Site 4601, UCSD
~~Daniel Szpak, RN, CCRC~~
~~Study Coordinator~~
~~UCSD Mother-Child-Adolescent HIV Program~~
~~4076 Third Avenue, Suite 301~~
~~San Diego, CA 92103~~
~~Phone: (858) 534-9216~~
~~Email: dszpak@ucsd.edu~~

Megan Loughran B.A.
Study Coordinator
4076 Third Avenue, Suite 301
San Diego, CA 92103
Phone: (858)-534-9218
Email: meloughran@ucsd.edu

Clarification Memorandum #2 for:

IMPAACT 2002
Combined Cognitive Behavioral Therapy and a Medication Management Algorithm for Treatment of Depression among Youth Living with HIV in the United States

Version 1.0, dated 19 August 2016
DAIDS ES # 12051

Clarification Memorandum Date: 4 October 2017

Summary of Clarifications and Rationale

The primary purposes of this Clarification Memorandum (CM) are:

1. To clarify that the Off-Study Form (F1601) may only be completed for participants that enrolled in the study.
2. To clarify that if the 1-Week visit occurs on the same day as the Screen/Entry visit, COMB-R sites must complete both the ACASI and paper QIDS-SR questionnaire.
3. To specify use of Version 2.1 of the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events for grading severity of adverse events in IMPAACT 2002 (instead of Version 2.0).
4. To update the Protocol Team Roster to reflect current membership and responsibilities.

Implementation

This Clarification Memorandum (CM) has been approved by the NIAID and NICHD Medical Officers. Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the sponsor prior to implementation; however, sites may submit it to the responsible IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.

The contents of the CM do not impact the sample informed consent forms for the study or the benefit-to-risk ratio for study participants. This CM should be maintained in each site's essential documents file for IMPAACT 2002. It is the responsibility of the Investigator of Record to ensure that all study staff are made aware of and follow this CM. The content of this CM will be incorporated into any future amendment of the IMPAACT 2002 protocol.

The modifications included in this CM are listed by modification. Deletions in the protocol text are indicated by ~~strikethrough~~ and additions shown in **bold** text.

1. To clarify that an Off-Study Form should only be completed for enrolled participants who are no longer able to participate in the study, a correction to the text included in CM #1 is made below.

   Section 4.4 Recruitment, Screening and Enrollment Process, 3rd Paragraph, CM #1, #6

   6. Once ~~consented~~ **enrolled**, if a participant is no longer able to participate in the study, an Off-Study Form will be completed.

2. *Updated Section 6.2 1 Week Visit to clarify the procedures to be completed if the Week 1 visit occurs on the same day as Entry.*

   The 1-Week Visit is targeted to take place on Day 7, counted from the date of enrollment as Day 0, with an allowable window of -7 and +14 days. Sites may conduct the 1-Week visit procedures on the same day as the Screen/Entry visit, if the participant and site staff have adequate time. If the 1-Week Visit is conducted on the same day as the Screen/Entry visit, then sites should not repeat procedures, such as ~~the QIDS-SR and~~ collecting medical and medication history. The primary purpose in this case, would be to provide therapy and medication management as indicated below. **Note per Section 5.3.2, if the 1-Week visit occurs on the same day as Entry, COMB-R sites must complete both the ACASI and paper QIDS-SR questionnaire; ESC sites are not required to repeat the QIDS-SR.** If the 1-Week Visit is not conducted on the same day as Screen/Entry, then all the procedures listed below must be performed.

3. *Updated protocol Section 7.4.3 to specify the use of Version 2.1 of the DAIDS Table for grading severity of adverse events*

   The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), ~~Version 2.0, dated November 2014~~ **Corrected Version 2.1, dated July 2017**, will be used to grade the severity of most adverse events in this study. This table is available on the RSC website at: ~~http://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf?sfvrsn=8~~ **http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables.**

4. *Updated the Protocol Team Roster to reflect current membership:*

   Clinical Trials Specialists
   ~~JL Ariansen, MS~~ **Anna LeViere, MPH**
   IMPAACT Operations Center, FHI 360
   359 Blackwell Street, Suite 200
   Durham, NC 27701, USA
   Phone: ~~(919) 544-7040 x11185~~ **919-475-11585**
   Email: ~~jariansen@fhi360.org~~
   ALeViere@fhi360.org

   Westat Clinical Research Associate
   ~~Rita Patel, MS~~ **Aundria Charles**
   Westat, Inc.
   1441 W. Montgomery Ave.
   Rockville, MD 20850
   Phone: (240) 453-~~2693~~ **2758**
   Email: ~~ritapatel@westat.com~~
   AundriaCharles@westat.com

   Protocol Data Managers
   ~~Elise Tjaden, MPH~~ **Chelsea Krotje, MPH**
   Frontier Science & Technology Research Foundation
   4033 Maple Road
   Amherst, NY 14226-1056
   Phone: (716) 834-0900 x ~~7272~~ **7368**
   Email: ~~tjaden@fstrf.org~~ **krotje@fstrf.org**

   Laboratory Data Managers
   ~~Kaitley Wozer, BS~~ **Frederic Bone**
   Frontier Science & Technology
   Research Foundation
   4033 Maple Road
   Amherst, NY 14226
   Phone: (716) 834-0900 x~~7224~~ **7306**
   Email: ~~wozer@fstrf.org~~ **bone@fstrf.org**

Clarification Memorandum #1 for:

IMPAACT 2002
Combined Cognitive Behavioral Therapy and a Medication Management Algorithm for Treatment of Depression among Youth Living with HIV in the United States

Version 1.0, dated 19 August 2016
DAIDS ES # 12051

Clarification Memorandum Date: 6 March 2017

Information/Instructions to Study Sites

This Clarification Memorandum (CM) has been approved by the NIAID and NICHD Medical Officers. Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the study sponsor prior to implementation. However, sites may submit this CM to the responsible IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.

The content of the CM does not impact the sample informed consent forms for the study or the benefit-to-risk ratio for study participants.

This CM should be maintained in each site's essential documents file for IMPAACT 2002. It is the responsibility of the Investigator of Record (IoR) to ensure that all study staff are made aware of this CM. The content of this CM will be incorporated into any future amendment of the IMPAACT 2002 protocol.

Summary of Clarifications and Rationale

The purpose of this CM is to: 1) clarify the study recruitment, screening and enrollment processes with respect to defining the scenarios in which a site will submit a Screening Failure and Non-Enrollment Results Form 2) clarify the forms specific to the Clinician Satisfaction Scales and 3) update the Protocol Team and Site Roster.

Implementation

The modifications included in this CM are listed below by update and in order of appearance in the protocol and will be incorporated into the next protocol amendment as specified below. Additions to the text are indicated in **bold**; deletions are indicated by ~~strikethrough~~.

1. Clarification of the screening and enrollment processes for potential participants

Section 4.4 Recruitment, Screening and Enrollment Process, 3rd Paragraph

It is expected that site staff will approach all potentially eligible youth for possible study participation. Patients will be recruited, and proceed with the screening process as follows:

[…]

3. Sites may **approach** ~~start screening and enrolling~~ anyone from their first block of screening numbers. Patients from the subsequent blocks may not be approached until all patients from the previous block are enrolled or have been approached but will not enroll into the study (for any reason). **If a patient is interested in the study, they will undergo the informed assent/consent process and be assigned a PID.**
4. ~~If a patient is interested in the study, they will undergo the informed assent/consent process and be assigned a PID.~~ **Sites will submit a "Screening Failure and Non-Enrollment Results Form" using the screening number in the following circumstances: 1)** If a **potential participant** ~~patient~~ is approached but not interested in enrolling in the **study, in this case, only the fact that the participant does not want to consent to the study will be recorded; 2) If a potential participant is approached and is interested in being in the study, but fails the eligibility criteria; in this case, the** ~~This~~ form will collect the reason(s) for not enrolling (i.e., ineligibility~~, refusal,~~ and associated reasons for ineligibility ~~or refusal~~), in addition to the patient's gender, race, **ethnicity,** age, viral suppression status, depression severity estimate, and mode of transmission. This record will not include **other** patient-identifying data.
5. When a **participant** ~~patient~~ is enrolled into IMPAACT 2002, the screening number, in addition to the eligibility criteria, will be entered into the data base. The DMC randomization system will verify that the screening number is on the list. Enrollment will occur upon successful entry of required eligibility data into the SES. Successful entry into the SES will generate a study identification number (SID).
6. **Once consented, if a participant is no longer able to participate in the study, an off-study form will be completed.**

2. Clarify the forms to be completed as part of the clinician satisfaction measures

Section 5.3.8 Clinician Satisfaction Scales, 4th and 5th paragraphs

At the COMB-R sites, the clinician conducting the H&W CBT sessions will complete a **six** ~~seven~~ item survey **(H&W CBT Clinician Satisfaction Questionnaire)** to assess the appropriateness, effectiveness, flexibility, ease of use, and "fit" of the H&W CBT treatment approach for the patient and the clinic (responses: Excellent, Good, Fair, Poor).

At the ESC sites, the clinician conducting the counseling sessions will complete a **five** ~~seven~~ item survey **(Counseling Clinician Satisfaction Questionnaire)** to assess the appropriateness, effectiveness, flexibility, ease of use, and "fit" of their treatment strategies for the patient and the clinic (responses: Excellent, Good, Fair, Poor).

Section 6.4 24 Week Follow-up Visit

24 Week Visit Procedures Study Day 168 (+/- 14 days)		
Behavioral and Counseling		• Administer QIDS-SR • Administer behavioral questionnaire • Administer Client Satisfaction Questionnaire • Administer ~~Physician~~ **Prescribing Clinician** Satisfaction Questionnaire ~~(COMB-R Sites Only)~~

Clinical		• Collect/update medical and medications history; including assessments for suicidality and number of kept and missed medical and mental health visits
		• Assess CDC HIV disease category
		• Identify/review/update adverse events (signs, symptoms, diagnoses)
		• COMB-R Sites Only:
		  • Administer CBT Session and complete the CBT Adherence Checklist
		  • Administer the MM Session and complete the MM Checklist
		  • **Complete H&W CBT Clinician Satisfaction Questionnaire**
		• ESC Sites Only:
		  • Psychotherapy as indicated by symptoms
		  • Medication management as indicated by symptoms
		  • Complete the ESC therapy Checklist
		  • **Complete Counseling Clinician Satisfaction Questionnaire**

Laboratory	**Blood**	*Collect blood for:* • CD4+ T-Cell Count^ • HIV-1 RNA^ • Plasma storage, for inflammatory markers

Appendix I: Schedule of Evaluations for All Participants

Study Visit	Week 24
Visit Window	±14 d
Behavioral and Counseling	
Site Prescribing Clinician ~~Physician~~ Satisfaction Questionnaire ~~(COMB-R Sites Only)~~	X
Clinical	
COMB-R Sites ONLY:	
H&W CBT Clinician Satisfaction Questionnaire	**X**
ESC Sites ONLY:	
Counseling Clinician Satisfaction Questionnaire	**X**

Have re-named "Physician Satisfaction Questionnaire" to "Site Prescribing Clinician Satisfaction Questionnaire" and removed (COMB-R sites only).

*Have added the following line for COMB-R Sites ONLY: "*H&W CBT Clinician Satisfaction Questionnaire." To be completed at Week 24 only.

*Have added the following line for ESC Sites ONLY: "*Counseling Clinician Satisfaction Questionnaire." To be completed at Week 24 only.

3. Updates to Protocol Team and Site Roster.

Protocol Data Managers
~~Michael Basar, BA~~ **Elise Tjaden, MPH**
Frontier Science & Technology Research Foundation
4033 Maple Road
Amherst, NY 14226-1056
Phone: (716) 834-0900 x~~7271~~ **7272**
E-mail: ~~basar.michael@fstrf.org~~
tjaden@fstrf.org

Study Site Roster Updates
~~Site 4001, Chicago Children's~~
~~Melanie Koch, LPC~~
~~Health and Wellness CBT~~
~~Lurie Children's Memorial Hospital~~
~~225 East Chicago Ave Box 155~~
~~Chicago, IL 60611-2605~~
~~Phone: (312) 227-8269~~
~~Email: mkoch@luriechildrens.org~~

Site 5040, The Research Foundation of SUNY-Stony Brook University Medical Center
Michele Kelly, CPNP, NPP
Study Coordinator
Department of Pediatrics
Stony Brook University School of Medicine
Stony Brook, NY 11794-8225
Phone: (631) **632-3736** ~~444-8832~~
Email:
Michele.kelly@stonybrookmedicine.edu

Site 5030, Emory University School of Medicine
Chandra C. Graves, PhD, ABPP
Department of Psychiatry and Behavioral Sciences
Emory University School of Medicine
Pediatric Infectious Disease Program
Atlanta, GA 30307
Phone: (404) 616-9380
Email: ccgrave@emory.edu

LaTeshia Thomas-Seaton, RN, BSN, CCRC
Children's Healthcare of Atlanta
Grady-Family and Youth Clinic at Ponce
341 Ponce de Leon Avenue, Room 201
Atlanta, GA 30308
Phone: (404) 616-5936
Email: leaston@emory.edu

Site 5052, The Regents of the University of Colorado
Daniel Reirdan, MD
Director, Combined Internal Medicine-Pediatrics Residency
Sections of Adolescent Medicine and Infectious Disease
Center for Bioethics and Humanities
13123 East 16th Avenue, Box 025
Aurora, CO 80045
Phone: (720) 777-4971
Email:
Daniel.reirdan@childrenscolorado.org

Amber Bunch, MA, LPC, LAC
Mental Health and Substance Abuse Specialist
Children's Hospital of Immunodeficiency Program (CHIP)
13123 East 16th Avenue, Box 055
Aurora, CO 80045
Phone: (720) 777-6758

Email:
amber.bunch@childrenscolorado.org

Site 5083, Rush University Medical Center
Ixchell Ortiz-Estes, RN, MSN
Study Coordinator
2020 W. Hrrison
Chicago, IL 60612
Phone: (312) 572-4541
Email: iortiz-estes@cookcountyhhs.org

Site 5013, Jacobi Medical Center
Michael G. Rosenberg, MD, PhD
Jacobi Medical Center
1400 Pelham Parkway South
Building #1, Suite 1W5
Bronx, NY 10461
Phone: (718) 918-4677
Email: michael.rosenberg@nbhn.net

Joanna Dobroszycki, MD
Jacobi Medical Center
1400 Pelham Parkway South
Building #1, Suite 1W5
Bronx, NY 10461
Phone: (718) 918-4667
Email: Joanna.dobroszycki@nbhn.net

~~Jacobo Abadi, MD~~
~~Pediatrician~~
~~Jacobi Medical Center~~
~~1400 Pelham Parkway South~~
~~Building #1, Suite 1W5~~
~~Bronx, NY 10461~~
~~Phone: (718) 918-4108~~
~~Email: Jacob.abadi@nbhn.net~~

IMPAACT 2002

Combined Cognitive Behavioral Therapy and a Medication Management Algorithm for Treatment of Depression among Youth Living with HIV in the United States

A Study of the International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Sponsored by:
The National Institute of Allergy and Infectious Diseases
Eunice Kennedy Shriver
National Institute of Child Health and Human Development
National Institute of Mental Health

DAIDS ES #12051
Non-IND Study

Protocol Chair:	Larry Brown, M.D.
Protocol Vice-Chairs:	Patricia Emmanuel, M.D. Betsy Kennard, Ph.D.
NIAID Medical Officer:	Ellen Townley, MSN, FNP Adeola Adeyeye, M.D., MPA
NICHD Medical Officer:	Sonia Lee, Ph.D.
Clinical Trials Specialists:	Kathryn Lypen, MPH JL Ariansen, MS

Version 1.0
19 August 2016

IMPAACT 2002
Combined Cognitive Behavioral Therapy and a Medication Management Algorithm for Treatment of Depression among Youth Living with HIV in the United States

TABLE OF CONTENTS

IMPAACT 2002
Combined Cognitive Behavioral Therapy and a Medication Management Algorithm for Treatment of Depression among Youth Living with HIV in the United States

ABBREVIATIONS AND ACRONYMS

AACAP	American Academy of Child and Adolescent Psychiatry
ACASI	Audio Computer-Assisted Self Interview
AE	Adverse event
AIDS	Acquired Immunodeficiency Syndrome
APA	American Psychological Association
ARV	Antiretroviral
ATN	Adolescent Trials Network
CAP/CLIA	College of American Pathologists/Clinical Laboratory Improvement Amendments
CBT	Cognitive Behavioral Therapy
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
COMB-R	Combined CBT and medication - revised
CRF	Case report form
CSQ-8	Client Satisfaction Questionnaire
DAIDS	Division of AIDS
DAIDS PRO	Division of AIDS Protocol Registration Office
DAERS	DAIDS Adverse Event Reporting System
DE	Design effect
DIC	Diffuse intravascular coagulation
DMC	Data Management Center
DSM-IV/V	Diagnostic and Statistical Manual of Mental Disorders
EAE	Expedited Adverse Event
EC	Ethics committee
EIA	Enzyme-linked immuno assay
ESC	Enhanced Standard Care
FDA	(U.S.) Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FSTRF	Frontier Science and Technology Research Foundation
FTFI	Face-to-Face Interviews
GCP	Good Clinical Practices
H&W CBT	Health and Wellness Cognitive Behavioral Therapy
HCG	Human chorionic gonadotropin
HIV	Human Immunodeficiency Virus
IATA	International Air Transport Association
ICC	Intra-cluster correlation coefficient
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IRB	Institutional review board
IoR	Investigator of Record
LAR	Legally authorized representative
LC	Laboratory Center
LDMS	Laboratory Data Management System

LPC	Laboratory Processing Chart
MAOI	Monoamine oxidase inhibitors
MI	Motivational Interviewing
MM	Medication Management
MOH	Ministry of Health
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NMS	Neuroleptic malignant syndrome
OCSO	Office of Clinical Oversight
OHRP	Office for Human Research Protection
PEPFAR	President's Emergency Plan for AIDS Relief
PID	Participant Identification Number
QIDS	Quick Inventory of Depression Symptomatology
QIDS-C	Quick Inventory of Depression Symptomatology - Clinician
QIDS-SR	Quick Inventory of Depression Symptomatology - Self report
RNA	Ribonucleic acid
RSC	Regulatory Support Center
SAE	Serious Adverse Event
SD	Standard Deviation
SDMC	Statistical Data Management Center
SES	Subject Enrollment System
SID	Study Identification Number
SIP	Site Implementation Plan
SMC	Study Monitoring Committee
SMFQ	Short Moods and Feelings Questionnaire
SNRI	Serotonin and norepinephrine reuptake inhibitors
SSRI	Serotonin reuptake inhibitor
SOP	Standard Operating Procedure
SoE	Schedule of Evaluations
SR	Self-report
SS	Serotonin syndrome
STI	Sexually transmitted infection
TAU	Treatment as usual

IMPAACT 2002
Combined Cognitive Behavioral Therapy and a Medication Management Algorithm for Treatment of Depression among Youth Living with HIV in the United States

PROTOCOL TEAM ROSTER

Protocol Chair
Larry K. Brown, MD
Director of Child, Adolescent, and Young Adult Psychiatry Research
Department of Psychiatry, Rhode Island Hospital
Professor, Alpert Medical School of Brown University
167 Point St., Suite 161
Providence, R.I. 02903
Phone: (401) 793-8808
Email: larry_brown@brown.edu

Protocol Vice-Chairs
Patricia Emmanuel, MD
Lewis A. Barness Endowed Chair
Professor and Chair of Pediatrics
USF Health; Morsani College of Medicine
2 Tampa General Circle, 5th Floor, Rm 5016
Tampa, FL 33606
Phone: (813) 259-8867
Email: pemmanue@health.usf.edu

Beth D. Kennard, Psy.D
University of Texas
Southwestern Medical Center
5323 Harry Hines Boulevard
Dallas, TX 75390-8589
Phone: (214) 456-4244
E-mail: beth.kennard@utsouthwestern.edu

NIAID Medical Officers
Ellen Townley, MSN, FNP
International Maternal Adolescent Pediatric Branch, DAIDS/NIAID/NIH
5601 Fishers Lane, Rm 8B37
Rockville, MD 20852-9831
Phone: (240) 292-4784
Fax: (240) 627-3465
Email: ellen.townley@nih.gov

Adeola Adeyeye, MD, MPA
Prevention Science Program, DAIDS, NIAID,
NIH Room 8B36 MSC 9831, 5601 Fishers Lane
Rockville, MD 20852-9831
Phone: (240) 669- 5005
BB: (240) 421-8446
Email: adeola.adeyeye@nih.gov

NICHD Medical Officer
Sonia Lee, PhD
Maternal and Pediatric Infectious Disease Branch
6100 Executive Blvd, Rm 4B11K
Bethesda, MD 20892
Phone: (301) 594-4783
Email: sonia.lee@nih.gov

NIMH Medical Officer
Susannah Allison, PhD
Scientific Program Officer
Infant, Child, & Adolescent Research Programs
NIMH Division of AIDS Research
5601 Fishers Lane, 9E26, MSC 9831
Rockville, MD 20582-9831
Phone: (240) 627-3861
Email: Susannah.Allison@nih.gov

Clinical Trials Specialists
Kathryn Lypen, MPH
IMPAACT Operations FHI 360
359 Blackwell St
Durham, NC 27701
Phone: (919) 544-7040, Ext. 11684
Email: klypen@fhi360.org

JL Ariansen, MS
IMPAACT Operations Center, FHI 360
359 Blackwell Street, Suite 200
Durham, NC 27701, USA
Phone: (919) 544-7040 x11185
Email: jariansen@fhi360.org

Protocol Statisticians
Miriam Chernoff, PhD
Center for Biostatistics in AIDS Research
Harvard T.H. Chan School of Public Health
651 Huntington Avenue
Boston, MA 02115
Phone: (617) 432-0358
Email: mchernoff@sdac.harvard.edu

David Shapiro, PhD
Center for Biostatistics in AIDS Research
Harvard T.H. Chan School of Public Health
651 Huntington Avenue
Boston, MA 02115
Phone: (617) 432-2426
Email: shapiro@sdac.harvard.edu

Statistical Programmer
Shirley Traite, MSW
Center for Biostatistics in AIDS Research
Harvard T.H. Chan School of Public Health
651 Huntington Avenue
Boston, MA 02115-6017
Phone: (617) 432-0073
Email: traite@sdac.harvard.edu

Protocol Data Managers
Michael Basar, BA
Frontier Science & Technology Research Foundation
4033 Maple Road
Amherst NY 14226-1056
Phone: (716) 834-0900 x7271
E-mail: basar.michael@fstrf.org

Jenna Kearly, MPH
Frontier Science & Technology Research Foundation
4033 Maple Road
Amherst, NY 14226-1056
Phone: (716) 834-0900 x7249
E-mail: kearly.jenna@fstrf.org

Laboratory Data Managers
Kaitley Wozer, BS
Frontier Science & Technology
Research Foundation
4033 Maple Road
Amherst, NY 14226
Phone: (716) 834-0900 x7224
Email: wozer@fstrf.org

Laura J. Hovind, MS
Frontier Science & Technology
Research Foundation
4033 Maple Road
Amherst, NY 14226
Phone: (716) 834-0900 x7468
Email: hovind@fstrf.org

Central Laboratory Specialist
Diane Costello
Children's Hospital of Los Angeles
4546 Sunset Blvd.
Smith Research Tower, Room 902Los Angeles, CA 90027
Phone: (703) 862-0820Email: dcostello@impaactlabcenter.org

Laboratory Technologist
Bill Kabat
Infectious Disease Laboratory, Ann & Robert H. Lurie Children's Hospital of Chicago
225 East Chicago Avenue, Box 82
Chicago, Illinois 60611
Phone: (312) 227-6291
Email: bkabat@luriechildrens.org

Protocol Immunologist
Adriana Weinberg, MD
Professor of Pediatrics, Medicine and Pathology
Medical Director of the Molecular and Virology Clinical Laboratories
University of Colorado Denver Anschutz Medical Center
Mail Stop: 8604
12700 East 19th Ave. Room 11126
Aurora, CO 80045
Phone: (303) 724-4480
E-mail: adriana.weinberg@ucdenver.edu

Westat Clinical Research Associate
Rita Patel, MS
Westat, Inc.
1441 W. Montgomery Ave.
Rockville, MD 20850
Phone: (240) 453-2693
Email: ritapatel@westat.com

Investigators
Graham Emslie, MD
University of Texas
Southwestern Medical Center
5323 Harry Hines Boulevard
Dallas, TX 75390-8589
Phone: (214) 456-5921
E-mail: graham.emslie@utsouthwestern.edu

Laura Whiteley, MD
Clinical Director of Young Adult Behavioral Health
Department of Psychiatry, Rhode Island Hospital
Assistant Professor, Alpert Medical School of Brown University
167 Point St., Suite 161
Providence, R.I. 02903
Phone: (401) 793-8808
Email: lbwhiteley@gmail.com

Community Program Manager
Cheryl D. Cokley, BS
FHI 360
359 Blackwell St., Suite 200
Durham, NC 22701, USA
Phone: (919) 544-7040 x11359
Email: ccokley@fhi360.org

Community Advisory Board Member
Leslie Raneri
Texas Children's Hospital
6621 Fannin St
Houston, TX 77071
Phone: (832)689-4845
Email: lraneri@hotmail.com,
lgraneri@texaschildrens.org

STUDY SITE ROSTER

Site 5114, Bronx-Lebanon Hospital Center
Murli Purswani, MD
Principal Investigator
Bronx Care Center for Comprehensive Care
1650 Selwyn Avenue
9th Floor
Bronx, NY 10457
Phone: (718) 579-5337
Email: mpurswan@bronxleb.org

Martha Cavallo, PNP
Study Coordinator
722 W 168th St
Suite 820
New York, NY 10032-3727
Phone: (866) 463-2778
Email: mcavallo@bronxleb.org

Site 5055, Children's Diagnostic and Treatment Center
Patricia A. Garvie, PhD
Psychologist
Children's Diagnostic & Treatment Center
1401 S. Federal Highway
Fort Lauderdale, FL 33316
Phone: 954-728-1032
Email: pgarvie@browardhealth.org

Ana M. Puga, MD, FAAP
CFAP Medical Director
Children's Diagnostic & Treatment Center
1401 S Federal Highway
Fort Lauderdale, Florida 33316
Phone: 954-728-1017
Email: apuga@browardhealth.org

Site 5030, Emory University School of Medicine
Andres Camacho-Gonzalez, MD
Principal Investigator
Family & Youth Clinic at Ponce, Room 201
341 Ponce de Leon Avenue NE
Atlanta, GA 30308
Phone: (404) 616-9786
Email: ACAMAC2@emory.edu

Bridget Wynn, MPH
Study Coordinator
Family & Youth Clinic at Ponce, Room 201
341 Ponce de Leon Avenue NE
Atlanta, GA 30308
Phone: (404) 966-1487
Email: Bridget.wynn@emory.edu

Site 5052, The Regents of the University of Colorado
Carrie Chambers, RN
Study Coordinator
B055
Department of Pediatric Infectious Disease
Children's Hospital of Colorado
13123 East 16th Ave
Aurora, CO 80045
Phone: (720) 777-4424
Email:carrie.chambers@childrenscolorado.org

Kimberly Pierce, DNP, RN, CPNP
Site Clinician, Medication Management
B055
Department of Pediatric Infectious Disease
Children's Hospital of Colorado
13123 East 16th Ave
Aurora, CO 80045
Phone: (720) 777-2870
Email: kimberly.pierce@childrenscolorado.org

Site 6501, St Jude Children's Research Hospital
Sandra Boyd, RN, MSN, CPNP
Study Coordinator
262 Danny Thomas Place, MS 600
Memphis, TN 38105
Phone: (901) 595-5059
Email: sandra.boyd@stjude.org

Megan Wilkins, PhD
Investigator of Record
262 Danny Thomas Place, MS 600
Memphis, TN 38105
Phone: (901) 595-5965
Email: megan.wilkins@stjude.org

Site 5040, The Research Foundation of SUNY-Stony Brook University Medical Center
Michele Kelly, CPNP, NPP
Study Coordinator
Department of Pediatrics
Stony Brook University School of Medicine
Stony Brook, NY 11794-8225
Phone: (631) 444-8832
Email: Michele.kelly@stonybrookmedicine.edu

Site 5013, Jacobi Medical Center
Andrew Wiznia, MD
Principal Investigator
Jacobi Medical Center
1400 Pelham Parkway South
Building #1, Suite 1W5
Bronx, NY 10461
Phone: (718) 918-4664
Email: Andrew.wiznia@einstein.yu.edu

Marlene Burey, PNP
Site Coordinator
Jacobi Medical Center
1400 Pelham Parkway South
Building #1, Suite 1W5
Bronx, NY 10461
Phone: (718) 918-4783
Email: marlene.burey@nbhn.net

Jacobo Abadi, MD
Pediatrician
Jacobi Medical Center
1400 Pelham Parkway South
Building #1, Suite 1W5
Bronx, NY 10461
Phone: (718) 918-4108
Email: Jacob.abadi@nbhn.net

Ray Shaw, PhD
Psychologist
Jacobi Medical Center
1400 Pelham Parkway South
Building #1, Suite 1W5
Bronx, NY 10461
Phone: (718) 918-4589
Email: ray.shaw@nbhn.net

Site 5048, The University of Southern California- MCA Center
Mikhaela Cielo, MD
Investigator of Record
1000 S. Freemont Avenue
Unit 62, Bldg. A
10N Suite 200
Alhambra, CA 91803
Phone: (323) 226-4619
Email: mikhaela.cielo@usc-mca.org

Yvonne Morales, LVN
Study Coordinator
1000 S. Freemont Avenue
Unit 62, Bldg. A
10N Suite 200
Alhambra, CA 91803
Phone: (626) 457-5861
Email: ytr@usc.edu

Site 3801, Texas Children's/Baylor
Chivon McMullen-Jackson, RN, BSN, CCRP
Study Coordinator
Texas Children's Hospital/Baylor College of Medicine
Department of Immunology, Allergy & Rheumatology
1102 Bates Ave., Suite 330
Houston, TX 77030
Phone: (832) 824-1339
Email: cdmcmull@texaschildrens.org

Site 4001, Chicago Children's
Melanie Koch, LPC
Health and Wellness CBT
Lurie Children's Memorial Hospital
225 East Chicago Ave Box 155
Chicago IL 60611-2605
Phone: (312) 227-8269
Email: mkoch@luriechildrens.org

Site 5092, Johns Hopkins University School of Medicine
Allison Agwu, MD, ScM, FAAP, FIDSA
PI, JHU IMPAACT and ATN
Johns Hopkins University School of Medicine
200 North Wolfe Street, Rm 3145
Baltimore, MD 21287
Phone: (410) 614-3917
Email: ageorg10@jhmi.edu

Thuy Anderson, RN, BSN
Research Nurse Manager
Johns Hopkins University
200 N Wolfe St
Suite 3147
Baltimore, MD 21287
Phone: (443) 287-8942
Email: tander34@jhmi.edu

Aleisha Collinson-Streng, RN, ACRN
IMPAACT Nurse Study Coordinator
Johns Hopkins University
200 N Wolfe St.
Suite 3096
Baltimore, MD 21287
Phone: (443) 287-8888
Email: Acolli14@jhmi.edu

Site 5083, Rush University Medical Center
Mariam Aziz, MD
Principal Investigator
2020 W. Harrison
Chicago, IL 60612
Phone: (312) 942-4265
Email: mariam-aziz@rush.edu

Maureen McNichols, RN, MSN
Study Coordinator
2020 W. Harrison
Chicago, IL 60612
Phone: (312) 572-4541
Email: Maureen_mcnicols@rush.edu

Katie Howe, MSW
Therapist
2020 W. Harrison
Chicago, IL 60612
Phone: (312) 572-4541
Email: khowe@cookcountyhhs.org

Site 5112, David Geffen School of Medicine at UCLA
Jaime Deville, MD
Principal Investigator
UCLA Department of Pediatrics
Division of Infectious Diseases
10833 Le Conte Ave, MDCC 22-442
Los Angeles, CA 90095
Phone: (310) 206-6369
Email: jdeville@mednet.ucla.edu

Michele Carter, RN
Study Coordinator
UCLA Department of Pediatrics
Division of Infectious Diseases
10833 Le Conte Ave, MDCC 22-442
Los Angeles, CA 90095
Phone: (310) 206-6369
Email: mfcarter@mednet.ucla.edu

Shellye Jones, LCSW
Mental Health Clinician
UCLA Department of Pediatrics
Division of Infectious Diseases
10833 Le Conte Ave, MDCC 22-442
Los Angeles, CA 90095
Phone: (310) 206-6369
Email: sdjones@mednet.ucla.edu

Site 4601, UCSD
Stephen A. Spector, MD
Investigator of Record
Director, Mother-Child-Adolescent HIV Program
University of California, San Diego
La Jolla, CA 92093-0672
Phone: (858) 534-7055
Email: saspector@ucsd.edu

Daniel Szpak, RN, CCRC
Study Coordinator
UCSD Mother-Child-Adolescent HIV Program
4076 Third Avenue, Suite 301
San Diego, CA 92103
Phone: (858) 534-9216
Email: dszpak@ucsd.edu

IMPAACT 2002
Combined Cognitive Behavioral Therapy and a Medication Management Algorithm for Treatment of Depression among Youth Living with HIV in the United States

SCHEMA

Purpose:	To examine if a Health and Wellness Cognitive Behavioral Therapy and Medication Management (COMB-R) intervention for depression demonstrates improved outcomes for HIV-infected youth in the United States
Design:	Multi-site, two-arm, cluster-randomized study
Study Population:	HIV-infected youth, ages 12 to 24 years, diagnosed with nonpsychotic depression
Sample Size:	Approximately 14 sites will be randomized. A total of 156 participants will be enrolled to achieve at least 140 evaluable for primary study outcomes. The sample size may be increased to achieve a sufficient number of evaluable participants, if the percentage of non-evaluable participants or the intracluster correlation coefficient turn out to be higher than assumed for the sample size calculations
Study Intervention:	Sites will be assigned to provide either COMB-R or Enhanced Standard of Care (ESC) to enrolled participants for 24 weeks
Study Duration:	Approximately 36 months total; accrual is expected to require approximately 24 months and each enrolled participant is expected to complete approximately 48 weeks of follow-up

Primary Objectives

- To evaluate whether the Health and Wellness Cognitive Behavioral Therapy and Medication Management Algorithm (COMB-R) treatment for depression is associated with improved depression outcomes at 24 weeks, compared to Enhanced Standard Care (ESC)
- To evaluate whether COMB-R is associated with improved biological measures of health over 24 weeks, including CD4 cell numbers and copies of HIV RNA in plasma compared to ESC

Secondary Objectives

- To assess whether COMB-R is associated with improved adherence for HIV and depression treatment compared ESC for the first 24 weeks and whether any differences are maintained at 48 weeks
- To assess whether differences in depression treatment outcomes are maintained at 48 weeks
- To assess whether demographic, behavioral, and biological factors could moderate the efficacy of COMB-R compared to ESC arms
- To assess whether COMB-R is associated with improved behavioral risk outcomes (alcohol/drug use; sex-risk behaviors) compared to those on ESC at Week 24 and Week 48
- To describe the implementation fidelity at COMB-R sites and the counseling strategies and medication patterns at ESC sites
- To describe and compare the number of interim visits, the frequency of medication use, and acceptability of COMB-R and ESC among participants and clinicians

- To compare the frequency and types of Grade 3 or higher Adverse Events, psychological hospitalizations and suicide attempts between COMB-R and ESC arms

1 INTRODUCTION

1.1 Background

Depression is common in patients with Human Immunodeficiency Virus (HIV). The majority of studies suggest that rates of psychiatric disorders, particularly mood disorders, are higher in patients with HIV than in the general population. In a study of 2,032 youth aged 14 to 24 living with HIV and in medical care, 21% had depression (1). In a study examining psychiatric care among 2,864 adults with HIV, 26% had sought individual or family treatment, 27% had regularly taken medication for depression, anxiety, or other emotional problems, and over 40% had discussed emotional problems with their medical provider (2, 3). Vitiello (3) further reported that among those taking antidepressants, 63% were taking at least one other psychotropic medication, suggesting that patients with HIV have significant difficulties with emotional disturbance, often requiring treatment beyond a single antidepressant. In the study by Bing, participants younger than 35 years old had a higher chance of having major depression, dysthymia, generalized anxiety disorder, or panic attacks (4), suggesting that younger age may be associated with increased risk of depression and other psychiatric disorders.

A full understanding of the mechanisms leading to depression in HIV-infected individuals is currently lacking. HIV infects glial cells of the central nervous system promoting local inflammation and cell destruction (5, 6). However, the systemic inflammatory component of HIV infection may play an additional role in its neurologic complications, just as it is a major determinant of other end-organ disorders. Animal models and studies of HIV-infected and uninfected individuals support the notion that systemic inflammatory factors may contribute to depression and other mood disorders (7-10) (11, 12). Conversely, depression also interferes with the treatment of HIV infection creating the potential of a vicious cycle in which individuals may fail to adhere to treatment regimens.

Children and youth infected with HIV at birth have additional factors, both biologic and environmental which may contribute to psychopathology. IMPAACT P1055, a prospective, longitudinal cohort study performed at 29 U.S. sites, found that 27% reported psychiatric symptoms that interfered with functioning. Although rates were comparable to a peer comparison group which included youth uninfected with HIV who were either perinatally exposed to HIV or were living in a household with an HIV-infected member (including some who were siblings of youth in the HIV-infected cohort), HIV positive youth were more likely to have received psychotropic medications and counseling, perhaps due to greater contact with medical care facilities (13).

As in medically healthy individuals, depression leads to decreased functioning and poorer outcomes in patients with HIV. Several studies have shown that depression interferes with adherence to HIV treatment, increases caregiver burden, increases healthcare costs, and decreases quality of life. Thus, addressing depressive disorders is essential for improving both psychiatric and medical outcomes for those living with HIV. In a retrospective cohort study over a three-year period, it was found that of 3,359 adults receiving HIV care, 42% (n=1398) had a diagnosis of depression and 15% (n=508) were receiving selective serotonin reuptake inhibitor (SSRI) treatment. In the 12 months after initiation of antiretroviral treatment, the study demonstrated that depressed adults had significantly decreased medical adherence and reduced ability to achieve an HIV viral load below 500 copies/mL than non-depressed patients (p=0.02). Depressed patients who were being treated with an antidepressant showed similar medical outcomes (adherence and viral load) to non-depressed patients, and significantly better outcomes than depressed patients not receiving antidepressant medication (14). Controlled trials and reviews indicate that treatment with SSRI medications can also lead to improved CD4 T-cell counts (14). Research into whether treating the depressive disorder leads to similar results in younger age groups is needed, particularly given that this age group has such a high rate of non-adherence to ARV treatment.

Current APA Practice Guidelines recommend treatment interventions for depression in persons living with HIV similar to those for non-medically ill patients with depression, albeit with increased attention to the potential drug-drug interactions with antidepressants (15). In those who are HIV-uninfected a combination of psychiatric medication and psychotherapy is recommended. The use of both a medication algorithm and cognitive behavioral therapy (CBT) has been shown to be most effective for the treatment of moderate and severe depression in a number of clinical trials and is considered the gold standard for treatment (16, 17). Studies in the U.S. and abroad suggest that collaborative care using measurement-based evidenced-based clinical decisions are effective for the treatment of chronic diseases, including depression (18, 19). Unfortunately, this standard of care (CBT and a medication algorithm in a collaborative care model) is often not practiced. Psychopharmacologic treatment algorithms for depression in non-infected individuals are often not followed in treatment settings because of the concern of clinicians about drug-drug interactions or idiosyncratic opinions about the efficacy of specific medications. Medication guidelines and CBT tailored for youth living with HIV do not exist for the treatment of depression. In addition, CBT is often unavailable for patients (16, 20) and CBT tailored for youth living with HIV (e.g. focusing on adherence, coping with medical illness, stigma) is not uniformly available or tested. For example, in the IMPAACT Network, only three of the 33 U.S. sites that were polled during the development of the study indicated that they are currently using a structured CBT manual, and the same number indicated that a medication management algorithm was used for treatment of depression. Only two sites indicated that both practices were used simultaneously. Finally, no IMPAACT site queried reported utilizing CBT or a medication algorithm that was adapted or tailored to the unique needs of HIV-infected patients.

1.2 Prior Research

The Adolescent Medicine Trials Network (ATN) 080, which concluded in October 2013, is the one other intervention study combining a medication algorithm and cognitive behavioral therapy in a stepped-care framework for the treatment of depression in youth living with HIV. This study will build on results from ATN 080. As shown in Table 1 below, the mean age of the 42 participants in ATN 080 was 21 years, and most were behaviorally-infected males. The four sites were randomly assigned to either the combination treatment condition (COMB) or to treatment as usual (TAU).

ATN 080 participants:

- Mean age: 21.5 (range 18-24)
- Male: 69% (COMB 95%, TAU 40%) statistically significant difference between conditions
- Black: 83%
- Hispanic: 21%
- Behaviorally-acquired HIV: 90%
- CD4 < 500: 52%
- Viral load < 400: 50%

At baseline, participants were judged by clinicians and by self-report to have moderate to severe depression as measured by validated scales. Outcomes on the major endpoints are shown below.

Table 1
Depressive Symptom Outcomes

	Baseline		Week 12		Week 24		Week 48	
	COMB	TAU	COMB	TAU	COMB	TAU	COMB	TAU
Measure	N=22	N=20	N=19	N=19	N=20	N=20	N=17	N=15
QIDS* – Clinician (S.D.)	15.4 (4.4)	14.1 (4.1)	6.9 (4.3)	N/A	2.1 (2.6)	10.4 (5.5)	N/A (1.8)	N/A
QIDS* – Self-report (S.D.)	15.5 (4.9)	15.4 (4.0)	7.4 (4.4)	11.0 (5.6)	4.3 (2.9)	11.1 (4.6)	4.1 (3.5)	10.2 (5.5)
Response rate (QIDS*↓≥50%)	—	—	52.6%	21.1%	85.0%	20.0%	88.2%	33.3%
Beck Hopelessness Scale (S.D.)	10.3 (4.1)	8.3 (3.8)	5.9 (4.5)	7.5 (5.7)	4.8 (3.6)	6.1 (3.3)	3.6 (1.8)	6.0 (3.7)

*QIDS = Quick Inventory of Depression Symptomatology

Analyses examined the effect of condition on the outcomes over time, adjusting for baseline values and gender. Overall, the analyses indicated that participants in the COMB intervention reported significantly fewer symptoms of depression at all follow-up points (all $p < .0001$), and exhibited a response to treatment three to four times of that reported by those in the TAU condition. The effects were maintained at Week 48, which was 24 weeks after the intervention concluded. Similar changes were seen in the clinician scores for depression at Week 24, which was the primary endpoint of the study (clinician data was not collected beyond 24 weeks). Participants in the COMB intervention also reported significantly less hopelessness over time than did those in the TAU condition. There were no differences between conditions in the scores on Life Satisfaction Scale or CD4 but scores changed in the expected direction. Among those with a detectable HIV viral load at baseline, reduction in viral load was associated with reduction in depressive symptoms, although there was no difference based on condition.

This study builds on the demonstration of efficacy of COMB found in ATN 080 by: (1) testing a "core component" version of COMB that retains all of the essential elements of the collaborative, stepped care intervention but is adapted for easy implementation and dissemination (COMB-R), (2) examining the impact of COMB-R on biological and medical adherence outcomes with a larger sample with greater power to detect differences than was available in the ATN trial, and (3) examining potential moderators of the intervention's impact, which could not be examined in the ATN study. Specifically, this trial will be able to examine the impact of gender, transmission category, and initial level of depression because it will enroll more females, younger ages (and

therefore more youth who are perinatally infected) and those with milder depressive symptoms than did ATN 080. In addition, the project will collect data on the number of interim visits to judge the impact of mental health treatment sessions. Data on these factors need to be collected in U.S. IMPAACT sites prior to the development of guidelines for the treatment of depression in youth living with HIV and prior to the translation and cultural adaptation that will be needed for interventions internationally.

1.3 Rationale

Depression is prevalent among youth living with HIV. While approximately 8% of the general adolescent population develops depression, prevalence among adolescents and young adults living with HIV has been reported as high as 50% (14, 21-23). HIV-infected individuals who have depression have poorer outcomes, not only with regard to functioning and life satisfaction, but also with medical outcomes. Studies indicate that depression leads to reduced adherence to HIV treatment and in turn HIV illness progression. Treatment of depression leads to improved life satisfaction, improved treatment adherence, and reduced illness progression (24). Although depression among youth living with HIV is prevalent and detrimental to treatment outcomes, little research has been conducted on the treatment of depression among HIV-infected adolescents and young adults.

In non-HIV infected populations there is significant evidence supporting the use of depression treatment strategies that combine psychiatric medication and therapy. Specifically, the utilization of both medication algorithms and cognitive behavioral therapy has been shown to be most effective for the treatment of moderate and severe depression in a number of clinical trials (25). However, simply extrapolating from depression trials in non-infected individuals is insufficient when providing treatment for HIV-infected youth. Individuals living with both HIV and depression are a unique population and present distinct diagnostic difficulties (e.g. symptoms common to both depression and HIV-related illnesses), as well as medical treatment issues (e.g. drug-drug interactions). Furthermore, adolescents with HIV present with additional and unique hurdles during treatment for depression compared to adults. This age group responds differently than adults to antidepressant treatments (e.g. lower response rates) (26) and adherence to mental health treatment (problematic in medically healthy youth) is further complicated and magnified by frequent treatment non-adherence associated with youth living with HIV. In addition, studies consistently indicate that CBT should be tailored for important developmental, cultural and contextual factors (27-29).

CD4 cell numbers and HIV plasma RNA burden are key measures of HIV disease progression. AIDS and non-AIDS adverse events, including neurocognitive disorders, are more common in HIV-infected individuals with low CD4 cell counts and high HIV plasma RNA burden. In this study we will determine the association of depression with CD4 cell numbers at entry and at nadir, HIV plasma RNA burden at entry and CDC category. However, depression is associated with low adherence to antiretroviral medication contributing to HIV disease progression. Thus, CD4 cell counts and HIV plasma RNA burden at the end of this study will be used as outcome measures, to test the hypothesis that an effective treatment of depression will improve adherence and consequently decrease HIV replication and increase CD4 cell counts.

The role of inflammation in neurocognitive disorders, including depression, is becoming increasingly recognized. Both in HIV-infected and uninfected individuals, high levels of C reactive protein, IFN alpha, fibrinogen, sP-selectin and IL6 have been associated with the development of depression and other neurocognitive disorders. Furthermore, in HIV-infected individuals, inflammation as measured by sCD14, IL1 beta, IL 6, di-dimers, TNF alpha, CCL10 and VCAM1 in the blood compartment and at mucosal sites has been shown to be a major component of HIV pathogenesis (30-33). Thus, inflammation and depression may synergize in HIV-infected individuals, further increasing morbidity. Inflammation may respond to interventions that improve adherence to and effectiveness of antiretroviral treatments.

Recent studies of HIV-infected individuals on ART uniformly show that the majority of adverse clinical outcomes with high morbidity and mortality are currently non-AIDS related (34-37). In the current treatment era, increased plasma inflammatory biomarkers are the best predictors of non-AIDS serious adverse events, morbidity and mortality of HIV-infected individuals (38-40). Thus, decreasing inflammatory biomarkers is extremely important in association with any intervention that aims at improving the long-term prognosis of HIV-infected individuals. Therefore, we will study the effect of the neuro-behavioral interventions planned in this protocol on plasma inflammatory biomarkers.

The intervention to be evaluated in this study is a treatment for depression that includes manualized Health and Wellness Cognitive Behavioral Therapy (H&W CBT) for youth living with HIV and Medication Management using an algorithm (MM). The H&W CBT addresses the unique challenges faced by this population. The intervention, utilizing collaborative care, evidence-based strategies (H&W CBT and MM) for youth living with HIV, will be compared to Enhanced Standard Care (ESC) for depression at selected IMPAACT sites. The study will examine whether participants receiving a tailored, evidenced-based and stepped-care treatment for depression (H&W CBT and MM) demonstrate improved depression and medical outcomes compared to participants receiving ESC.

1.4 Hypotheses

1) Participants receiving COMB-R will demonstrate improved depression outcomes (e.g., decreased depressive symptoms, and greater remission and response rates) compared to participants receiving ESC.

2) Participants receiving COMB-R will demonstrate improved medical outcomes (e.g., increased CD4 T-cell count, decreased HIV RNA level) compared to participants receiving ESC.

2 OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are to:

2.1.1 To evaluate whether the Health and Wellness Cognitive Behavioral Therapy and Medication Management Algorithm (COMB-R) treatment for depression is associated with improved depression outcomes at 24 weeks, compared to Enhanced Standard Care (ESC).

2.1.2 To evaluate whether the COMB-R is associated with improved biological measures of health over 24 weeks, including CD4 cell numbers and copies of HIV RNA in plasma compared to ESC.

2.2 Secondary Objectives

The secondary objectives of this study are to:

2.2.1 To assess whether COMB-R is associated with improved adherence for HIV and depression treatment compared to ESC for the first 24 weeks and whether any differences are maintained at 48 weeks.

2.2.2 To assess whether differences in depression treatment outcomes are maintained at 48 weeks.

2.2.3 To assess whether demographic, behavioral, and biological factors could moderate the efficacy of COMB-R compared to ESC arms

2.2.4 To assess whether COMB-R is associated with improved behavioral risk outcomes (alcohol/drug use; sex-risk behaviors) compared to those on ESC at Week 24 and Week 48

2.2.5 To describe the implementation fidelity at COMB-R sites and the counseling strategies and medication patterns at ESC sites.

2.2.6 To describe and compare the number of interim visits, the frequency of medication use, and acceptability of COMB-R and ESC among participants and clinicians

2.2.7 To compare the frequency and types of Grade 3 or higher Adverse Events, psychological hospitalizations and suicide attempts between COMB-R and ESC arms

2.3 Exploratory Objectives

The exploratory objectives of this study are to:

2.3.1 To examine whether COMB-R is associated with a larger decrease in plasma inflammatory biomarkers from entry to Weeks 24 and 48 compared to ESC

2.3.2 To evaluate the moderating effect of inflammatory markers on the efficacy of COMB-R compared to ESC.

3 STUDY DESIGN

IMPAACT 2002 study is a prospective, multi-site, two-arm cluster-randomized study of the efficacy of a cognitive-behavioral intervention (COMB-R) for depression in youth with HIV compared to enhanced standard care (ESC). Youth enrolled in the study will attend a Screening/Entry Visit and study visits at Weeks 1, 6, 12, and 24. They will have two additional follow-up visits at Weeks 36 and 48 for the study team to evaluate if observed effects of the intervention are maintained.

Approximately 14 U.S. IMPAACT sites will be randomly assigned to either the COMB-R group or the ESC group. Randomization of sites was chosen due to the potential contamination that could occur if same site clinicians were delivering both ESC and COMB-R. A pre-study survey will ascertain various characteristics, such as number of youth served, gender, age (12-18 versus 19-24 years of age), viral suppression status (below versus not below the level of detection as defined by the laboratory), transmission routes (perinatal versus behavioral HIV acquisition), initial levels of depression (moderate vs. severe), and whether site IRBs will allow a parental waiver of consent. A restricted randomization procedure will be used to assign sites to the two study arms in a way that balances these characteristics across arms (based on the pre-study survey). The protocol team will also monitor the balance of these characteristics in the two study arms (blinded to which arm is which) on a quarterly basis, or as needed, and may impose limits on enrollment of participants with one or more of the specific characteristics noted above, if it is determined that any of these characteristics of the study arms are becoming unbalanced. Further details on the randomization procedure and criteria for adjusting enrollment at sites are provided in Section 9.0. The protocol includes several design features to minimize selection bias, including defining eligibility criteria that apply equally to both study arms; requiring sites to obtain screening numbers for all potentially eligible participants and randomizing the order in which the site will approach potential participants for enrollment; and collecting limited data on patients who do not enroll so that their characteristics can be compared to those of participants who did enroll (to assess the potential extent of selection bias). New randomized lists will be created for sites as needed.

Selected sites will have the capacity to enroll at least eight participants over the two years of enrollment and to perform assessments listed in Section 6.0 of the protocol. They will also have a mental health clinician, who will be trained in H&W CBT, treat youth between the ages of 12 and 24 and their families, attend a monthly phone supervision call, and treat approximately three participants in weekly H&W CBT. The sites also have access to a licensed prescriber (MD or LNP, etc.) who will be trained in the MM algorithm, attend monthly conference calls, and follow the MM guidelines. A clinician will be available to verify the diagnosis of depression and clinical eligibility criteria at time of enrollment. COMB-R sites will have the capacity to obtain the QIDS-SR from the patient and provide the score to the clinician at the time of the medication management visit.

4 STUDY POPULATION

The study population will be HIV-infected youth with depression, who meet criteria outlined in Sections 4.1 and 4.2.

4.1 Inclusion Criteria

Potential participants must meet all of the following criteria in order to be included in this study:

4.1.1 Age 12 through 24 years (inclusive)

4.1.2 Receiving mental health or HIV-related care at participating U.S. IMPAACT sites

4.1.3 Confirmation of HIV-1 Infection

Has confirmed HIV-1 infection based on testing of two samples (whole blood, serum, or plasma) collected at different time points:

Sample #1 may be tested using any of the following:

- Two rapid antibody tests from different manufacturers or based on different principles and epitopes
- One EIA or Western blot OR immunofluorescence assay OR chemiluminescence assay
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid test

Sample #2 may be tested using any of the following:

- One rapid antibody test. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved and the third rapid test must be from a third manufacturer or based on a third principle or epitope.
- One EIA OR Western blot OR immunofluorescence assay OR chemiluminescence assay
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid test

If both samples are tested using antibody tests, at least one of the samples must be tested in a laboratory that operates according to Good Clinical Laboratory Practice (GCLP) guidelines and participates in an appropriate external quality assurance program. If nucleic acid testing is used, at least one test must be performed in a CLIA certified or equivalent laboratory. For tests performed in other settings, adequate source documentation including the date of specimen collection, date of testing, test performed, and test result must be available.

4.1.4 Participant aware of his or her HIV infection, as determined by site staff

4.1.5 Per clinician assessment, primary diagnosis of nonpsychotic depression, including Major Depressive Disorder, Depression NOS, or Dysthymia, as defined by DSM-IV or DSM-V criteria

4.1.6 Current depressive symptoms that warrant intervention as determined by a score of ≥ 11 on the Quick Inventory of Depressive Symptomatology – Clinician (QIDS-C)

4.1.7 Able to communicate in spoken and written English

4.1.8 Able and willing to provide written informed assent/consent and able to obtain written parental or guardian permission (if required, as specified in site SOP, by State law, and/or IRB policy) to be screened for and to enroll in IMPAACT 2002

4.2 Exclusion Criteria

Potential participants who meet any of the following criteria will be excluded from this study:

4.2.1 Known or self-reported by participant to have a history of any psychotic disorder and/or bipolar I or II disorder

4.2.2 Severe disorders (more than 6 symptoms) based on DSM-V criteria) related to alcohol, cannabis or other substances; or those with moderate symptoms (4 or 5 symptoms) who are also currently experiencing withdrawal or dependence symptoms; within the past month prior to enrollment

4.2.3 Per clinician assessment at screening, depression and/or suicidal ideation requiring more intensive treatment than the study provides or at immediate risk of being a danger to themselves or others

4.2.4 Per participant report at screening, intends to relocate away from the study site during study participation

4.2.5 Participant currently in therapy with a non-study provider, unless willing to switch to a study-trained provider

4.2.6 Has any other condition that, in the opinion of the Investigator of Record (IoR)/designee, would preclude informed assent/consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

4.3 Co-Enrollment Considerations

Co-enrollment in other studies is not precluded, although careful consideration must be given to issues such as eligibility criteria, visit burden, and interpretation of outcome data across studies. Given these considerations, requests for co-enrollment must be approved in advance by the Protocol Teams of both studies.

4.4 Recruitment, Screening, and Enrollment Process

After the sites are randomized to COMB-R or ESC (see Section 9.3), participants will be recruited in a systematic manner from among the potentially eligible HIV-infected youth patient population at each site. Sites should consider youth with or without a history of depression, those with or without a history of mental health treatment, and those currently in mental health treatment; providing they are thought to meet study eligibility criteria.

As noted in Sections 3.0 and 9.1, selection bias is a concern. The protocol includes several design features to minimize selection bias, including requiring sites to obtain screening numbers for all potentially eligible participants and randomizing the order in which the site will approach potential participants for enrollment; and collecting limited data on patients who do not enroll so that their characteristics can be compared to those of participants who did enroll (to assess the potential extent of selection bias). New randomized lists will be created for sites as needed

It is expected that site staff will approach all potentially eligible youth for possible study participation. Patients will be recruited, and proceed with the screening process as follows:

1. Sites create a list of all potentially eligible youth at their site and complete a Screening Log in the Subject Enrollment System (SES) for each patient from their list. Completion of the Screening Log will generate a screening number.
2. Prior to site initiation of formal screening and enrollment into the study, the Statistical Data Management Center (SDMC) will retrieve the lists of potential participants entered, and randomly order all of the screening numbers within each site into blocks. The DMC randomization department will load these blocks into the randomization system and send the blocks to the sites; the team will then notify sites that this process has been completed and that they can begin screening and enrollment.
3. Sites may start screening and enrolling anyone from their first block of screening numbers. Patients from the subsequent blocks may not be approached until all patients from the previous block are enrolled or have been approached but will not enroll into the study (for any reason).
4. If a patient is interested in the study, they will undergo the informed assent/consent process and be assigned a PID. If a patient is approached but not interested in enrolling in the study, the site will submit a Screening Failure Result Form using the screening number. This form will collect the reason(s) for not enrolling (i.e., ineligibility, refusal, and associated reasons for ineligibility or refusal), in addition to the patient's gender, race, age, viral suppression status, depression severity estimate, and mode of transmission. This record will not include patient-identifying data because they have not yet provided informed assent/consent for the study.
5. When a patient is enrolled into IMPAACT 2002, the screening number, in addition to the eligibility criteria, will be entered into the data base. The DMC randomization system will verify that the screening number is on the list. Enrollment will occur upon successful entry of required eligibility data into the SES. Successful entry into the SES will generate a study identification number (SID).

Ideally, screening and enrollment into the study will be conducted on one day, if the participant is willing and found to be eligible.

Ineligible participants may rescreen for study participation provided their initial reason for ineligibility has changed. In addition, those participants listed on the pre-screening list who do not screen for the study or do not enroll for any reason may be subsequently assigned new screening numbers, and new potential participants will be assigned screening numbers as they are identified. The SDMC will regularly retrieve the lists of potential participants and steps 2 through 5 above will be repeated as needed to achieve the target study enrollment.

The protocol team will provide site staff with standardized training on pre-screening and screening potential participants, such that patient characteristics are balanced across study arms. Refer to Section 9.5 for more information on monitoring participant accrual in this study.

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC).

4.5 Participant Retention

Once a participant is enrolled in IMPAACT 2002, the study site will make every effort to retain them in follow-up through their study end date. Optimally, participant retention procedures will be established such that loss rates do not exceed 15% of enrolled participants over the 48 weeks of follow-up, and do not exceed 10% during the first 24 weeks of follow-up. Study site staff are responsible for developing and implementing local standard operating procedures to target this goal. Refer to Section 9.5 for more information on monitoring participant retention in this study.

5 STUDY INTERVENTIONS

This study will not directly supply or distribute any ARVs or psychiatric medications to study participants. Details on the study intervention are included below for COMB-R (Section 5.1) and ESC (Section 5.2). Specific measures and assessments used across both arms are further explained in Section 5.3. Descriptive data on provider characteristics will be collected at all sites and may include the provider's position at the site, degree and specialty, years since degrees, years of HIV experience, years working with adolescents, and/or other similar characteristics.

5.1 COMB-R Study Sites

Therapists at COMB-R sites will provide behavioral therapy to participants as per the Cognitive Behavioral Manual. Health and Wellness (H&W) Cognitive Behavioral Therapy (CBT) and medication management treatment strategies have been developed specifically for youth living with both HIV and depression. H&W CBT is based on a relapse prevention CBT manual for treating youth with depression who are uninfected (41) and upon research on adults with HIV (42). H&W CBT uses problem-solving, motivational interviewing, and cognitive-behavioral strategies to decrease adherence obstacles and increase wellness. Further details on these manuals are provided in Sections 5.1.1 and 5.1.2 below. Participants will also complete behavior questionnaires and receive laboratory testing to monitor HIV disease progression.

5.1.1 Medication Management (MM) Manual

The MM manual includes guidance for clinicians on strategies and tactics to treat depression in this population, including factors to consider when deciding on treatments (i.e., drug-drug interactions, side effects). An algorithm will be used that specifies the order of the antidepressant medications to be used (with several options at each stage), length of time, and doses for antidepressant treatment, taking into consideration current and previous medications used for depression and their reported response. The algorithm was developed based on current practice guidelines for treating adolescent and young adult depression, as well as recommendations from the American Psychological Association (APA) guidelines for treating depression in participants with HIV. In addition, due to frequent side effects associated with HIV illness and treatments, it is likely many of these participants will have other symptoms associated with depression, such as anxiety, aggression/irritability, and severe sleep disturbance. Most medication treatment guidelines fail to address these symptoms. However, the MM manual includes components from algorithms used in completed trials with depressed and suicidal adolescents, which provide treatment options for associated symptoms such as these (43-45).

The algorithm provides a guideline for clinicians, which includes several treatment options; clinicians then have freedom to choose in which direction to take the participant. The algorithm is not intended to restrict the clinician; rather, it provides a framework by which to treat depressed adolescents and young adults based on the scientific data available. Clinicians will be expected to follow the algorithm, and if deviations from the algorithm are made, justification and documentation as to the reason for the deviation will be recorded on the Medication Management Checklist. Decisions concerning medication changes will be discussed on the monthly COMB-R medication management calls.

Clinicians often continue individuals on suboptimal doses or ineffective medications for too long or make medication changes too quickly without adequate opportunity for the initial medication to work. The algorithm will provide decision points throughout treatment intended to guide the clinician to evaluate whether treatment is sufficiently improving depressive symptoms and provides guidelines for alternative strategies if there is inadequate improvement.

Despite using treatments from general adolescent and adult depression populations, modifications have been made to address issues specific to adolescents and young adults living with HIV. Specifically, the manual includes:

1) A medication staged approach: The first stage of treatment in the MM manual is a non-medication stage (Stage 0) in which participants are monitored. If participants, their parent/guardian (if parental consent required), and clinician agree that their depressive symptom presentation does not warrant medication treatment, they may continue in this stage until a decision is made to initiate antidepressant treatment. The visit schedule will remain the same for participants who do not begin antidepressants so they can continue to be closely monitored for potential worsening of depression. It is possible that some participants will not require any medication for depression. Subsequent stages of the algorithm are based on using medications with the greatest efficacy and fewest side effects first, followed by medications with less empirical evidence and potential increased risk. Generally, Stage 1 includes SSRI medications, as these appear most efficacious with the fewest side effects. Subsequent stages will include an alternative SSRI, followed by other novel antidepressants (e.g., bupropion, venlafaxine). At each stage, participants with a partial response to the antidepressant may be prescribed augmenting agents (e.g., lithium, bupropion, and atypical antipsychotics) to enhance the treatment response. Additional stages will be provided, although there is less empirical evidence for these later stages.

Medications such as atypical antipsychotics and sleep aids may also be used to address associated symptoms, and recommended methods for implementing these medications are included in the manual. See Table 2 for an outline of the medication stages.

2) Psychoeducation about adherence: Adherence to medications in general is often a problem for adolescents and young adults with HIV. This population is required to take multiple medications, many of which cause significant side effects, and are expected to be taken indefinitely. Furthermore, depression often leads to reduced compliance with medication for medical conditions, which in turn causes worsening of medical symptoms, which can also lead to further depression. Compounding this issue, some youth will not want to take additional medications to treat depression on top of their HIV regimen. One component of the MM in this study will be education about the importance of compliance, both with the antidepressant treatment as well as ARV treatments. The H&W CBT therapist will provide more in depth education and motivational interviewing (MI) to improve adherence, while the site prescribing clinician will focus more on the medical impact of adherence and non-adherence.

3) Issues related to side effects associated with antidepressants and/or HIV medications: Another modification specific to HIV-infected adolescents and young adults is the role of potential antidepressant side effects. While the side effect profile of medications is always a consideration for individuals, regardless of medical status, it is a particularly guiding factor for those with serious medical conditions and/or chronic medication interventions. For example, weight loss is a common side effect associated with ARVs and their treatments. Some antidepressants are more known for causing weight gain (e.g., mirtazapine), and may serve not only as an antidepressant, but also to reduce weight loss. Other common side effects of ARVs and associated treatments that may be improved by different antidepressants include fatigue, insomnia, and nausea. The manual has been modified to include specific side effects associated with each of the antidepressants, a list of common side effects associated with ARVs and ARV treatments, and recommendations for specific antidepressants that may improve those symptoms.

4) Drug-drug interactions associated with the medication options: Drug-drug interactions among antidepressants and ARV treatments will need to be considered. The manual has been modified to include potential drug-drug interactions so physicians can avoid these combinations. A recent review by Yanofski and Croarkin (46) addresses safety and side effect issues related to treating depression concurrently with antiviral medications. Thus, study investigators have collaborated with Dr. Croarkin, as well as other experts and clinicians in the ATN, to address these issues in the manual. It is beyond the scope of this exploratory study to conduct formal pharmacokinetic analyses of relevant antidepressants and ARV treatments, so this study will rely on existing data and expert opinion to address the issues of drug-drug interaction.

Table 2
Stages of the Medication Algorithm for Depression

Stage	Treatment	Medication Options
Stage 0	No medication	N/A
Stage 1	Monotherapy with SSRI	Fluoxetine, citalopram, sertraline, escitalopram, paroxetine Partial responders after six weeks may receive augmentation with lithium, bupropion, or an atypical antipsychotic
Stage 2	Monotherapy with 2nd SSRI	Fluoxetine, citalopram, sertraline, escitalopram, paroxetine Partial responders after six weeks may receive augmentation with lithium, bupropion, or an atypical antipsychotic
Stage 3	Monotherapy with non-SSRI	Venlafaxine, bupropion, mirtazapine, duloxetine Partial responders after six weeks may receive augmentation with lithium, bupropion, or an atypical antipsychotic
Stage 4	Combination treatment	Two antidepressants or antidepressant plus lithium

5.1.2 Health and Wellness Cognitive Behavioral Therapy (H&W CBT) Manual

The H&W CBT manual may be flexibly used to address the individual needs of the participant. Thus, while the typical stages of treatment for a given participant are presented in Table 3 below, therapists will have the ability to adjust the sequence of the treatment as needed, as well as the ability to bring in treatment modules specific to other relevant clinical issues (e.g., anxiety, emotional regulation difficulties, and social skills deficits). These modules will be known as "Sequence Adjustment procedures." The three primary components presented in sequenced stages below include: (1) psychoeducation and motivation for treatment; (2) reducing depressive symptoms; and (3) achieving and maintaining wellness.

Table 3
H&W CBT Session Content

Treatment Stage	Stage Objectives	Week	Session Content
Stage 1 Psychoeducation and Motivation for Treatment	▪ Build rapport ▪ Educate about depression and HIV and the H&W CBT model ▪ Increase adherence	1-2	▪ Psychoeducation (participant and family, if appropriate) ▪ Mood monitoring ▪ Motivational interviewing component for increased adherence
Stage 2 Reducing Depressive Symptoms	▪ Reduce residual symptoms through core skills ▪ Assess and identify core beliefs ▪ Identify and increase areas of strength and wellness	3-8	▪ Psychoeducation about relapse risk ▪ Begin timeline ▪ Mood monitoring ▪ Behavioral coping skills ▪ Family module on negative emotion (as needed) ▪ Cognitive restructuring ▪ Core beliefs and positive self-schema ▪ Problem solving ▪ Individualized skill modules as needed ▪ Begin wellness assessment
Stage 3 Achieving and Maintaining Wellness	▪ Consolidation and further practice of core skills and wellness skills to manage mood ▪ Relapse prevention	10, 12, 14, 16	▪ Introduce concept of wellness ▪ Identify current strengths and areas of wellness needing improvement ▪ Practice and apply core and wellness skills for relapse prevention ▪ Relapse Prevention and Wellness Plan
Continuation	▪ Consolidation of treatment gains ▪ Evaluate/revise relapse prevention and wellness plans as needed	20, 24	▪ Content varies depending on participant's needs

1) Stage 1: Psychoeducation and Motivation for Treatment:

The H&W CBT treatment addresses the numerous psychosocial stresses of HIV infection and chronic medical care, as well as treatment of ongoing symptoms of depression. As noted above, there are several issues specific to HIV-infected adolescents and young adults that go beyond strict depression treatment. Specifically, these participants may be less committed to treatment for depression because the seriousness of their medical condition far outweighs that of depressive symptoms. Adolescents and young adults with HIV already are required to attend multiple medical appointments, and may be less likely to want to add additional visits with a therapist for depression treatment. In addition, adherence to antidepressant medication also may be problematic. Also, stressors such as poverty, stigma, and alienation from families may feel more pressing than the need for treatment. Therefore, the first portion of the H&W CBT is non-confrontational and includes Motivational Interviewing (MI) techniques to engage the adolescents

and young adults in psychotherapeutic care. The first two sessions will be devoted to psychoeducation and adherence promotion, both with regard to HIV and depression. Participants will be educated on the link between depression and medical conditions (i.e., the impact of depression on their condition and vice versa), relationship of depression and general functioning, and importance of reducing depression to improve daily functioning. In addition, because adherence to treatment is often a concern with chronic medical conditions, MI techniques will be used to improve compliance with both medical treatments and depression treatments (47-49).

Additionally, these initial sessions will serve as a period of establishing an alliance between the participant and the H&W CBT therapist and establishing specific areas of concern for the participant and therapist to focus on during the remaining stages. The manual also has flexibility in the session schedule, so that participants who would benefit from additional intervention to improve adherence can have more sessions devoted to these areas. In addition, during the course of treatment (six months), the therapist may return to these topics if the need arises (e.g., the participant has been noncompliant with medications).

2) Stage 2: Reducing Depressive Symptoms:

This module will include six sessions focused on reducing current symptoms (primarily depressive symptoms, although modules can be added for other comorbid symptoms such as anxiety as described above). The content of these sessions will focus on teaching the participant skills that reduce depressive symptoms. These core skills include mood monitoring, behavioral activation, reducing negative thinking, and problem-solving. As mentioned earlier, the participant may need more or less of these sessions depending on the level of symptomatology present. The manual is flexible, such that a participant with fewer symptoms may move more quickly to the wellness modules (Stage 3 below). On the other hand, participants with more clinical issues may have "Sequence Adjustment procedure" modules added to address these issues prior to moving to Stage 3.

3) Stage 3: Achieving and Maintaining Wellness:

Once depressive symptoms have significantly improved, the therapist and participant work together on identifying factors associated with enhancing wellness and preventing relapse. This module will continue through the final four sessions. Wellness enhancement will be an important area for HIV-infected adolescents and young adults, as they are likely to have become entrenched in the "patient" mode, particularly given their young age. Identifying and enforcing the areas in which they are "well" and "thriving" will allow them to build on personal strengths and adaptive behaviors. The focus of the sessions is on identifying the participant's current areas of strength, as well as targeting areas/behaviors for improving and enhancing wellness. During this stage, the participant and therapist will also work to identify factors that may lead to worsening of mood, and methods to prevent depression from returning. Again, these sessions will incorporate topics to address concerns associated with HIV and chronic illness.

5.2 ESC Study Sites

Participants at ESC sites will receive enhanced standard of care counseling. They will also complete behavior questionnaires and receive laboratory testing to monitor HIV disease progression. This study will assess the care provided at participating ESC sites by documenting the number of sessions of psychotherapy and medication management provided, the medications used by participants, provider characteristics, and mental health care accessed outside the research site.

5.2.1 ESC counseling

Patients will be screened and assented/consented as described above. In order for the study to have greater generalizability and external validity, psychopharmacological and psychosocial interventions will not be standardized but rather will reflect on-going treatment for depression at HIV clinical treatment centers. Participants may receive any depression treatment recommended by the site clinicians. Sites will use the clinicians who usually provide these services. The project will assess clinician degrees and length of HIV-related experience. Clinical coordinators will record attendance at medical and mental health visits and HIV illness outcomes.

Enhancement of standard of care counseling with up-to-date training on treatment of depression
The standard care arm is considered "enhanced" due to clinicians at ESC sites receiving updated didactic information from the study team, on the current principles for the use of medication and psychotherapy in the treatment of depression. This brief training will be relevant for clinicians and will include clinician rated instruments, but will not provide details on the medication management algorithm or tailored H&W CBT treatment used in COMB-R.

Training in clinical management for both groups will include how to assess current symptoms, and the impact of symptoms on level of function. In addition, training on the provision of supportive care—specifically involving those nonspecific elements of psychotherapy that are not considered CBT components (reflective listening, validation, supportive problem-solving) will be provided. Training will also be provided in the medication management of depressed youth. Specifically, trainers will review standard care practices, including the American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameters for the treatment of depression in youth. In addition, trainers will discuss how symptoms will be assessed at each treatment visit, and how to assess clinical outcomes using evidenced based measures.

5.3 Study Evaluations and Measures

Evaluations will include self-reported assessments collected via Audio Computer-Assisted Self Interview (ACASI) and/or interview administered forms, to document depressive symptoms, ARV medication adherence, risk behaviors, and consumer perspectives (i.e., satisfaction with intervention). ACASI is used in research studies to collect sensitive data, as studies have shown that participants may provide more accurate responses when questions are asked in a computer-assisted format. (50-53). ACASI allows for complex skip patterns so that participants only answer items that are relevant based on their earlier responses. Additional outcome measures will be collected via medical record abstraction, and face-to-face interviews (FTFI) to assess areas of functioning and symptoms (i.e., cognitions, conduct, satisfaction) and service utilization (i.e., treatments and adherence). Table 4 outlines the various measures used for each intervention arm. Assessments for participants in both arms will be conducted on entry and at 6, 12, 24, 36 and 48 weeks.

Table 4
Study Measures and Assessments by Study Arm

Measure	COMB-R Arm	ESC Arm
Quick Inventory Depressive Symptomatology – Clinician (QIDS-C)	X	X
Quick Inventory Depressive Symptomatology – Self Report (QIDS-SR)	X	X
Behavioral assessment; includes sexual behavior, alcohol and drug use, and adherence modules	X	X
ESC Therapist Checklist		X
H&W CBT Adherence Checklist	X	
Medication Management Checklist	X	
Client Satisfaction Questionnaire-8 (CSQ-8)	X	X
Clinician Satisfaction Scales	X	X

5.3.1 Quick Inventory Depressive Symptomatology – Clinician (QIDS-C)

A licensed mental health clinician will complete the QIDS-C, a scale assessing the symptoms of depression in the past seven days, via a FTFI at screening. The purpose of the QIDS-C at screening is to serve as a depression severity rating for eligibility. At subsequent study visits, the COMB-R clinicians will use the QIDS-SR to assess symptom change, which will be used to guide treatment decisions.

5.3.2 Quick Inventory Depressive Symptomatology – Self Report (QIDS-SR)

Participants will complete the Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR), a 17-item scale assessing nine depressive symptoms, at baseline and follow-up visits as described in Section 6.0. QIDS-SR is a reliable and valid measure of depression in adults and adolescents (54, 55). Total scores range from 0-27, whereby scores of 6-10 reflect mild symptoms, 11-15 moderate, and $\geq$16 severe. Score range and symptom severity categories are the same for the QIDS-C. QIDS-SR scores over time are used in two binary outcomes. Response to treatment is defined as a >50% decrease from baseline, and remission from depression is defined as a QIDS-SR score <5. Only the participant will complete the survey, and not the participant's parent or guardian. The QIDS-SR will be conducted via either ACASI or paper form as follows:

Study Visit	COMB-R Arm	ESC Arm
Baseline/Enrollment	ACASI	ACASI
Weeks 1, 6 and 12	Paper form	ACASI
Weeks 24, 36, and 48	ACASI	ACASI
Interim Visits	Paper form	NA

Notes:

1. When participants complete the QIDS-SR on paper, those data will be provided to the COMB-R clinicians in real-time. Data from ACASI will not be provided in real-time; however, clinicians at all sites will continue to assess for any changes in the participant's depression status during therapy sessions.

2. COMB-R sites that will complete QIDS-SR on paper, as indicated above, will enter the data from the paper QIDS-SR into the study database.

5.3.3 Behavioral Assessment

Risk behaviors will be assessed based on modules developed by the Adolescent Trials Network (ATN) Secondary Prevention and Adherence Workgroups. These items assess sexual risk behaviors, and drug and alcohol use. The adherence assessment will assess frequency and consistency of use of ARV and depression medications and attendance at therapy sessions. This scale will be administered via the ACASI at baseline and follow-up, per Section 6.0.

Substance use will be assessed with an abbreviated 24 item ASSIST, which was developed by the World Health Organization for use in medical care settings (56). Items used will assess lifetime history and frequency of past three-month use of nine classes of substances: tobacco, alcohol, cannabis, cocaine, stimulants, inhalants, sedatives, hallucinogens, and opioids on a five-point scale ("never" to "daily or almost daily"). In addition, quantity of alcohol and cannabis is assessed in the past three months. The ASSIST is a frequently used measure of substance use and has been found to be reliable and valid (57).

Sexual behavior will be assessed with 16 items from a more detailed assessment developed by the ATN Secondary Prevention Working Group. Items assess any lifetime history and past three-month frequency of occurrence of oral, vaginal and anal sex. Skip patterns allow for more detailed assessment of relevant behaviors such as number of sexual partners, frequency of condom use (vaginal and anal) and condom use with main and "other" partners, and condom use at the time substance use. Sexual orientation and gender of sexual partners is also assessed. The items assess behaviors most commonly measured in sexual risk reduction interventions and have been found to be associated with mental health symptoms and reflect the impact of behavioral interventions (58, 59).

Adherence to HIV and mental health treatment medications
Medication adherence assessment, to both depression medications and ARV, and counseling will occur during MM and ESC follow up visits to determine if changes in medication and dosing are needed based on improvement or lack of improvement of depressive symptom severity.

Clinicians providing treatment counseling during MM visits will utilize the MM algorithm as a framework to treat patients. Results from the participant self-report depressive symptoms survey, conducted at H&W CBT visits, will be shared with clinicians during MM visits.

Adherence to HIV and mental health treatment medications will also be measured via ACASI by three items. One item assesses the number of days in the past month when at least one dose was missed, and two assess the patient's perception of their frequency of adherence and their effectiveness at adherence on Likert-type scales ("very poor" to "excellent"). These items were found to have an internal consistency of 0.89 in a cognitive and field test to determine clarity, comprehension, and reliability characteristics among taking antiretroviral medications (60).

In addition to adherence questions asked via ACASI (described above), staff will review clinic records at baseline, 12, 24, 36 and 48 weeks to determine the number of kept and missed visits for medical and mental health (therapy or psychiatric medication evaluation or management) care in the IMPAACT clinic site in the past 12 weeks. The number of unscheduled visits for medical and mental health care during the 12 weeks will also be recorded. Visits scheduled and attended

during the 12 weeks, even if the visits were rescheduled, will be recorded as "kept". Participants self-report of adherence will also be assessed at the same time points.

5.3.4 ESC Therapy Checklist

ESC therapists will complete a checklist at the end of each session that documents the strategy used for that session, using a list of common categories of psychotherapy.

5.3.5 COMB-R Therapy Adherence Checklist

COMB-R therapists will complete a checklist at the end of each H&W CBT visit to document which elements of the intervention were delivered, and to record unique issues that arise.

5.3.6 Medication Management Checklist

At the end of MM visits, COMB-R site clinicians will list the participant's algorithm stage, clinical depression status, any changes to medication status, and deviations to the algorithm of participants participating in the intervention. ESC site clinicians will list the participant's current medication and any changes.

5.3.7 Client Satisfaction Questionnaire-8 (CSQ-8)

The CSQ-8 will be used at the completion of the intervention to assess the participant's satisfaction with the intervention, including the procedures, quality and quantity of service, outcome, and general satisfaction. These domains are assessed on a four-point response scale with individually specified anchors. In addition, three open-ended questions are included that solicit comments about what respondents liked most and least about the intervention. This scale will be administered via the ACASI.

5.3.8 Clinician Satisfaction Scales

Clinician satisfaction measures for clinicians at all sites will be completed via paper questionnaire.

At the COMB-R sites, the prescribing clinician will complete a short survey, at the completion of the intervention, about their experience with the algorithm treatment for each participant. The first section contains three questions, which are rated on a scale from "Strongly agree" to "Strongly disagree": 1) Following the algorithm was difficult with this participant; 2) Using the algorithm assisted me in making treatment decisions for this participant; and 3) The participant's symptoms have improved since starting the algorithm. The second section contains one question about the overall quality of the treatment using the algorithm (responses: Excellent, Very good, Good, Substandard, Unacceptable).

At the ESC sites, the prescribing clinician conducting medication management will complete a short survey, at the completion of the intervention, about their experience of treatment for each participant. The survey contains two questions, which are rated on a scale from "Strongly agree" to "Strongly disagree": 1) Following my medication treatment plan was difficult for this participant; 2) The participant's symptoms have improved since starting the medication treatment.

At the COMB-R sites, the clinician conducting the H&W CBT sessions will complete a seven item survey to assess the appropriateness, effectiveness, flexibility, ease of use, and "fit" of the H&W CBT treatment approach for the patient and the clinic (responses: Excellent, Good, Fair, Poor).

At the ESC sites, the clinician conducting the counseling sessions will complete a seven item survey to assess the appropriateness, effectiveness, flexibility, ease of use, and "fit" of their treatment strategies for the patient and the clinic (responses: Excellent, Good, Fair, Poor).

5.3.9 Other Assessment Considerations

This study will not assess for minor cognitive limitations, and as such, no measure of cognitive limitations will be utilized during screening or study follow-up. Based on ATN 080, there will unlikely be a moderating impact of minor cognitive impairment on the study's objectives. Furthermore, currently available measures were designed to assess cognitive limitations associated with aging and pre-Alzheimer's pathology, and have not been validated for children.

5.4 Intervention Monitoring/Quality Control

Study fidelity for both COMB-R and ESC sites will be accomplished through online or remote training on the assessment of depressive symptoms using the QIDS-C and SR ratings.

5.4.1 Quality Control for Medication Management Intervention Visits

The MM portion of the intervention will be monitored for quality control in the following ways:

On-line Training: Site prescribing clinicians will be trained by members of the study team, on the MM manual, algorithm, assessment of depression treatment history, assessment of depressive symptoms (QIDS-C and QIDS-SR ratings), and the use of these rating scales to optimize treatment (e.g., when to change dose or medication based on ongoing lack of response). Several vignettes will be used to develop a common culture for identifying treatment staging within the algorithm, which will be particularly important for participants entering the study already on an antidepressant medication (See Section 5.5).

Monthly Monitoring Calls with COMB-R Site Prescribers: The Protocol Chairs, and others as needed, will provide monthly MM supervision for all COMB-R site prescribers through a group conference call, and each participant entering the study will be reviewed on the call for deviations from algorithm staging. Any deviations will be documented on the Medication Management Checklist by prescribers. The Algorithm is not prescriptive. It provides a framework for decision-making. Site clinicians will make the final decisions as to the medication and doses prescribed. Ongoing cases with treatment concerns will also be reviewed on the call, and all clinicians will provide input as to the best treatment plans, thereby developing a common culture across sites. Sites may also contact the protocol team with any questions or comments that may arise in between conference calls.

MM Report: A report will be generated that contains the QIDS-SR scores, algorithm stage, antidepressant medications, augmenting medications, number of weeks on medication, clinical status, any side effects to antidepressants reported and additional psychotropics prescribed/indicated. The IMPAACT Statistical and Data Management Center will generate the report monthly initially, or as needed, for the protocol investigators to review participants' depression and medication status to ensure that the clinicians are following the algorithm.

5.4.2 Quality Control for Cognitive Behavioral Therapy Intervention Visits

The H&W CBT portion of the intervention will be monitored for quality control in the following ways:

On-line Training: H&W CBT therapists will be trained on the H&W CBT manual through didactic instruction, role plays, and/or vignettes. All sessions and assessments will be practiced to ensure consistency prior to intervention delivery (See Section 5.5).

Monthly Monitoring Calls with H&W CBT Therapists: The Protocol Chairs, and others as needed, will provide monthly supervision (or more frequent at study initiation) for H&W CBT therapists via H&W CBT group conference calls to discuss ongoing cases. Sites may also contact the protocol team with any questions or comments that may arise in between conference calls.

H&W CBT Adherence Checklist: The H&W CBT Adherence Checklist contains all the required items that must be covered in each H&W CBT visit. Site therapists will complete the adherence checklist after each H&W CBT visit. The DMC will provide all newly completed forms to the protocol chairs to review on the monthly calls with the clinicians. The Checklist will identify items in sessions that were difficult to address or were omitted so that these issues can be discussed on the calls.

5.4.3 Quality Control for ESC Visits

ESC therapists will complete a checklist at the end of each session that documents the strategy used for that session, using a list of common categories of psychotherapy. This measure will document procedures at the ESC sites, in order to be able to compare and contrast the treatment strategies of ESC with COMB-R.

5.5 Research Staff Training

Site prescribing clinicians, licensed mental health clinicians, therapists, study coordinators, and other research staff will engage in an online training. Site prescribing clinicians and therapists will have separate training sessions specific to their responsibilities, as outlined in Table 5 below:

Table 5
Training Session Responsibilities

Provider	Training Component	Training Method(s)	COMB-R Sites	ESC Sites
Site prescribing clinicians/licensed mental health clinicians	QIDS ratings	Didactic review; rating tapes; case vignettes	X	X
Site prescribing clinicians/licensed mental health clinicians	Medication manual (algorithm)	Didactic review; rating tapes; case vignettes	X	
Therapists	H&W CBT manual	Didactic review; watch videos; case vignettes for case conceptualization; review of core treatment strategies	X	
Therapists	Supportive Care, not considered CBT components	Didactic review	X	X
Therapists	Standard care practices, including the American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameters	Didactic review of practice parameters	X	X

5.6 Concomitant Medications

Enrolled study participants may use concomitant medications during study participation. All concomitant medications reported throughout the course of the study will be recorded on case report forms designated for that purpose. All prescription medications, over-the-counter preparations, vitamins, nutritional supplements, and herbal preparations will be recorded on forms for concomitant medications. If a female participant initiates use of antidepressants during the study, counseling will be provided on the risks of pregnancy while using these medications, as per standard clinical care.

6 STUDY VISITS AND PROCEDURES

An overview of study visits and evaluations is provided in Appendix I; blood draw volumes for each visit are also detailed in Appendix I. Presented in this section is additional information on visit-specific study procedures. All visit procedures must be conducted at the clinical research site, or associated facilities, identified in each site's approved site implementation plan (SIP) and must be documented in accordance with DAIDS policies for source documentation; refer to Section 10.0 for more information on documentation requirements. Refer to Section 7.0 for information on expedited adverse event reporting, which may be required at any time during follow-up. All procedures specified to be performed at scheduled visits should ideally be

performed on the same day. However, if this is not possible (e.g., if a participant must leave the clinical research site before all procedures can be performed), visits may be split, with procedures performed on more than one day within the allowable visit window.

In addition to the protocol-specified procedures listed in this section, study staff may complete other tasks consistent with site SOPs, including but not limited to collecting, reviewing, and updating demographic and locator information; reviewing elements of informed consent; scheduling telephone contacts and visits; providing instructions for contacting study staff between visits; providing visit reminders; and following up on missed visits. All such tasks should be documented consistent with site SOPs.

Participants at every COMB-R and ESC assigned site will attend a Screening/Entry Visit, and follow-up clinic visits at Weeks 1, 6, 12, 24, 36, and 48. In addition, participants in the COMB-R sites will be encouraged to return to the clinic for weekly therapy visits through Week 8, every other week through Week 16, and then monthly until Week 24. These visits are not mandatory, and will be considered and documented as interim visits. At these interim visits, study staff will conduct therapy utilizing the CBT manual, and provide medication management, utilizing the MM manual, as indicated. Participants in the ESC sites will likewise return to the clinic for interim visits, based on the clinical indication of the participant.

Further details and form instructions for these interim visits are provided in the IMPAACT 2002 study MOP. Requiring assessment visits at Weeks 1, 6, 12, 24, 36, and 48, while also allowing for flexibility in scheduling clinical interim visits, will demonstrate COMB-R management in realistic clinical settings. This will furthermore allow participants, approached to participate in the study at both COMB-R and ESC sites, to perceive a similar study burden and visit schedule. Following completion of the study, researchers will analyze the number of interim visits conducted at COMB-R and ESC sites, based on clinician and participant clinical needs, to better understand the amount of clinical visits needed to improve depression outcomes.

6.1 Screening and Entry Visit

Screening and enrollment procedures may be performed on the same day. Multiple visits may be conducted to complete all required screening procedures if necessary, and within 30 days of enrollment. Written informed assent/consent must be obtained before any screening procedures are performed. For potential participants who do not meet the eligibility criteria, screening may be discontinued once ineligibility is determined.

Screening and Entry Visit Procedures (Day 0)		
Administrative and Regulatory		• Obtain written informed consent; or written informed assent and parental or guardian consent, for Screening and Enrollment • Assign participant identification number (PID) • Collect demographic and locator information • Determination of eligibility • Complete paper-based eligibility checklist*, enter checklist data into SES to enroll the participant, print and file a copy of the confirmation file
Behavioral and Counseling		• Provide HIV pre-/post-test counseling* • Administer behavioral questionnaire • Administer QIDS-SR
Clinical		• Obtain medical and medications history; including assessments for suicidality • Assess CDC HIV disease category • Complete QIDS-C • Obtain CD4 nadir based on medical chart review
Laboratory	**Blood**	*Collect blood for:* • CD4+ T-Cell Count^ • HIV-1 RNA^ • Plasma storage, for inflammatory markers • HIV-1 test (confirmatory tests as needed)*

* If indicated; ^Documented laboratory results from an external provider that is CLIA-certified may be utilized for IMPAACT 2002, if the sample(s) was collected within 14 days of study entry

Note: if the screening and entry visit is split, sites must complete the following procedures at the entry visit: confirm eligibility, obtain an updated medical and medication history, collect laboratory specimens, and administer the baseline behavioral questionnaire, QIDS-SR and QIDS-C forms.

6.2 1 Week Visit

The 1-Week Visit is targeted to take place on Day 7, counted from the date of enrollment as Day 0, with an allowable window of -7 and +14 days. Sites may conduct the 1-Week visit procedures on the same day as the Screen/Entry visit, if the participant and site staff have adequate time. If the 1-Week Visit is conducted on the same day as the Screen/Entry visit, then sites should not repeat procedures, such as the QIDS-SR and collecting medical and medication history. The primary purpose in this case, would be to provide therapy and medication management as indicated below. If the 1-Week Visit is not conducted on the same day as Screen/Entry, then all the procedures listed below must be performed.

1 Week Visit Procedures Study Days 7 (-7/+14 days)	
Behavioral and Counseling	• Administer QIDS-SR

Clinical	• Collect/update medical and medications history; including assessments for suicidality and number of kept and missed medical and mental health visits
	• Identify/review/update adverse events (signs, symptoms, diagnoses)
	• COMB-R Sites Only:
	  • Administer CBT Session and complete the CBT Adherence Checklist
	  • Administer the MM Session and complete the MM Checklist
	• ESC Sites Only:
	  • Psychotherapy as indicated by symptoms
	  • Medication management as indicated by symptoms
	  • Complete the ESC therapy Checklist

6.3 6 and 12 Week Visits

The 6-Week Visit is targeted to take place on Day 42 with an allowable window of ± 14 days.
The 12-Week Visit is targeted to take place on Day 84 with an allowable window of ± 14 days.

6 and 12 Week Visit Procedures Study Days 42 (+/- 14 days), 84 (+/- 14 days)	
Behavioral and Counseling	• Administer QIDS-SR • Administer behavioral questionnaire

Clinical	• Collect/update medical and medications history; including assessments for suicidality and number of kept and missed medical and mental health visits
	• Identify/review/update adverse events (signs, symptoms, diagnoses)
	• COMB-R Sites Only:
	  • Administer CBT Session and complete the CBT Adherence Checklist
	  • Administer the MM Session and complete the MM Checklist
	• ESC Sites Only:
	  • Psychotherapy as indicated by symptoms
	  • Medication management as indicated by symptoms
	  • Complete the ESC therapy Checklist

6.4 24 Week Follow-up Visit

The 24-Week Visit is targeted to take place on Day 168 with an allowable window of ± 14 days.

24 Week Visit Procedures Study Day 168 (+/- 14 days)		
Behavioral and Counseling		• Administer QIDS-SR • Administer behavioral questionnaire • Administer Client Satisfaction Questionnaire • Administer Physician Satisfaction Questionnaire (COMB-R Sites Only)

Clinical		• Collect/update medical and medications history; including assessments for suicidality and number of kept and missed medical and mental health visits
		• Assess CDC HIV disease category
		• Identify/review/update adverse events (signs, symptoms, diagnoses)
		• COMB-R Sites Only:
		  • Administer CBT Session and complete the CBT Adherence Checklist
		  • Administer the MM Session and complete the MM Checklist
		• ESC Sites Only:
		  • Psychotherapy as indicated by symptoms
		  • Medication management as indicated by symptoms
		  • Complete the ESC therapy Checklist

Laboratory	**Blood**	*Collect blood for:* • CD4+ T-Cell Count^ • HIV-1 RNA^ • Plasma storage, for inflammatory markers

^ Documented laboratory results from an external provider may be utilized for IMPAACT 2002, if the sample(s) was collected in the visit window

6.5 36 and 48 Week Follow-up Visits

Following the Week 24 visits, participants in both COMB-R and ESC groups may receive counseling and psychiatric medication per individual clinician/patient decisions. Participants at all sites will have two follow-up visits, at Week 36 and Week 48, to monitor if the effects of the intervention were maintained. The Week 48 Visit will serve as the final clinic.

36 and 48 Week Follow-up Visit Procedures Study Days 252 and 336 (+/- 14 days)		
Behavioral and Counseling		• Administer QIDS-SR • Administer behavioral questionnaire
Clinical		• Collect/update medical and medications history; including assessments for suicidality and number of kept and missed medical and mental health visits • Assess CDC HIV disease category • Identify/review/update adverse events (signs, symptoms, diagnoses)
Laboratory	**Blood**	*Week 48 ONLY: Collect blood for:* • CD4+ T-Cell Count^ • HIV-1 RNA^ • Plasma storage, for inflammatory markers

^ Documented laboratory results from an external provider may be utilized for IMPAACT 2002, if the sample(s) was collected in the visit window

Sites should inform study participants that they will not continue to receive study-provided therapy through the study after their 24 Week Visit, but will continue with their therapist or be referred for care if needed. They will continue to return to the study site for study follow-up visits however to assess whether effects of the intervention are maintained. Sites should also arrange with participants to provide any laboratory test results obtained at the 48 Week Visit, as well as results of the study when available.

6.6 Interim Follow-up Visits

Participants in the COMB-R sites will be encouraged to return to the clinic for weekly interim therapy visits through Week 8, every other week through Week 16, and then monthly until Week 24. ESC sites will conduct interim visits, based on the clinical indication of the participant. Interim visits are not mandatory and will not be considered missed, if a participant is unable to attend the visit.

Interim Follow-up Visit Procedures	
Behavioral and Counseling	• Administer QIDS-SR (COMB-R Sites only)*

Clinical	• Collect/update medical and medications history; including assessments for suicidality*
	• Identify/review/update adverse events (signs, symptoms, diagnoses)
	• COMB-R Sites Only:
	  • Administer CBT Session and complete the CBT Adherence Checklist*
	  • Administer the MM Session and complete the MM Checklist*
	• ESC Sites Only:
	  • Psychotherapy as indicated by symptoms*
	  • Medication management as indicated by symptoms*Complete the ESC therapy Checklist*

*if indicated

6.7 Premature Discontinuation of Study Participation Visit

Any participant that terminates from the study early will be requested to return to the clinic to complete the final evaluations as specified for the Week 48 visit.

6.8 Procedures for Participants Who Become Pregnant

Pregnant participants may remain in the study and will continue all protocol-specific procedures, but will be counseled on discontinuing use of antidepressants in accordance with clinical judgment of site investigator and standard care practices. Additionally, if site staff suspect a female participant is at high risk for pregnancy, and she is currently using antidepressants, counseling will be provided on safety risks in accordance with the clinical judgment of the site investigator and standard of care practices.

Study sites will refer pregnant participants to providers of obstetric and gynecologic care for counseling and further related care. Every effort will be made to facilitate access to prevention of mother-to-child transmission regimens if the participant is not yet accessing ART. Study staff, with permission from the participant and, if required, the participant's parent and/or guardian, may contact the medical care provider to inform him/her of the participant's involvement in IMPAACT 2002.

HIV-1 infected women who are pregnant should be treated according to the Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Peri-natal HIV Transmission in the United

States: June 7, 2016 (https://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0#). Study sites will also be encouraged to prospectively register the participant's pregnancy in the Antiretroviral Pregnancy Registry. http://www.apregistry.com/ (In U.S.: 1-800-258-4263).

6.9 Additional Considerations for Laboratory Procedures

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials Policy, which is available at:
http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/Laboratories.aspx

6.9.1 Specimen Collection

Specimens will be collected for this study as indicated in the Schedule of Evaluations and per detailed guidance provided in the Laboratory Processing Chart (LPC), which will be available on the IMPAACT website: www.impaactnetwork.org.

In accordance with U.S. National Institutes of Health (NIH) recommendations, for pediatric patients, no more than 5 mL/kg may be drawn for research purposes in a single day, and no more than 9.5 mL/kg may be drawn over any eight-week period. The amount of blood that may be drawn from adult participants (i.e., those persons 18 years of age or older) for research purposes shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period. In the event that blood collection must be limited, available specimens should be prioritized for use in the following order: (1) CD4+ T-Cell Count and HIV-1 RNA, (2) plasma storage for inflammatory markers.

Each study site will adhere to the standards of good clinical laboratory practice in accordance with current DAIDS Laboratory Requirements, and site Standard Operating Procedures (SOPs) for proper collection at the local laboratory. In cases where laboratory results are not available due to administrative or laboratory error, sites are permitted to re-draw specimens.

6.9.2 Specimen Preparation, Testing, Storage, and Shipping

All specimens collected for this study will be labeled, transported, processed, tested, stored and/or shipped in accordance with the DAIDS policy referenced in Section 6.9, site and local laboratory SOPs, and the LPC. The Laboratory Data Management System (LDMS) will be used to document specimen collection, testing, storage, and shipping as specified in LPC.

CD4 and HIV RNA will be performed locally at CLIA certified or equivalent laboratories. Plasma in EDTA will be collected for inflammatory biomarkers and stored at -70ºC at the local laboratory. At the end of the study, samples will be shipped to a designated central laboratory for testing. Analytes will include hsCRP, d-dimer, IL1, IL6, IP10, sCD14 and TNF.

After all protocol-specified laboratory testing has been performed, residual specimens may be of interest for future research use. Participants (and authorized guardians if applicable) will be asked to provide written informed consent for future research use of these specimens, if permitted by site IRBs/ECs and other applicable review bodies. Participants and/or their guardians may choose to provide or to decline informed consent for future research use of residual specimens with no impact on their participation in the study.

6.9.3 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as recommended by the CDC and NIH. All biological specimens will be transported using packaging mandated by Code of Federal Regulations (CFR) 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

7 SAFETY ASSESSMENT AND REPORTING

An overview of the protocol-required safety assessment and reporting requirements for site investigators is provided below. Safety monitoring by the protocol team and the Study Monitoring Committee (SMC) is described in Section 9.5.

7.1 Safety-Related Roles and Responsibilities for Site Investigators

Site investigators are responsible for continuous monitoring of all study participants and for alerting the protocol team if unexpected concerns arise. Medical history, occurring within 30 days prior to enrollment, will be considered past medical history. These data will be graded to compare with worsening conditions during study follow-up, and to determine whether or not an AE has occurred, as indicated in Section 7.2. Site investigators will record safety-related events during follow-up on case report forms (CRFs) as indicated in Section 7.3 and complete expedited adverse event (EAE) reporting as indicated in Section 7.4. Site investigators are also responsible for prompt reporting to their IRBs/ECs and other applicable review bodies of any unanticipated problems involving risks to participants or others.

7.2 Recording of Pre-Existing Conditions

All pre-existing conditions, occurring within 30 days prior to enrollment and regardless of grade, will be recorded on case report forms as signs, symptoms, and diagnoses.

7.3 Safety Data on Case Report Forms

Grade 3 or higher adverse events, regardless of presumed relationship to study intervention, will be recorded on case report forms as signs, symptoms, and diagnoses as specified below. Additionally, all psychological hospitalizations, and suicide attempts will likewise be documented on CRFs. Sites will determine relationship status by considering whether the AE resulted from the COMB-R or ESC counseling procedures.

Signs and Symptoms: Grade 3 or higher signs and symptoms occurring after enrollment through study exit visit, which may or may not be related to the study counseling procedures, will be recorded on the relevant CRF. The site investigator will determine relationship status of each sign or symptom. In addition, Grade 4 signs and symptoms that occur after enrollment will be further evaluated, with additional data recorded on the relevant event evaluation CRF.

Diagnoses: Grade 3 diagnoses occurring after enrollment (through the study exit visit) will be recorded on the relevant CRF. The site investigator will determine relationship status of each diagnosis. Grade 4 or higher diagnoses that occur after enrollment will be further evaluated, with additional data recorded on the relevant event evaluation CRF. All diagnoses will be recorded on case report forms consistent with the specifications of the relevant diagnosis appendix, which is available at www.fstrf.org.

CRFs used to record the above-listed safety outcomes must be completed and entered into the study database within 21 calendar days from the date of the visit.

7.4 Expedited Adverse Event (EAE) Reporting

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

The study team will monitor and track unanticipated problems related to study counseling procedures until participants' time of termination from the study. Study staff will provide clinically appropriate treatment and/or referrals should any such problems occur.

7.4.1 Adverse Event Reporting to DAIDS

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at CRMSsupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

For Expedited Adverse Event (EAE) Reporting/Questions: Contact DAIDS through the RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 301-897-1709; or fax 1-800-275-7619 or 301-897-1710.

7.4.2 Reporting Requirements for this Study

The intervention for which expedited reporting is required is: the study counseling procedures.

The following types of events will be reported on an expedited basis for this study:

1. Suicide attempts
2. Psychological hospitalization

Note: Any event that occurs in a participant that is not necessarily a suicide attempt or psychological hospitalization, but in the opinion of the site investigator could cause harm to the participant or harm to others is also important for the study team to monitor. While these instances do not need to be recorded as an EAE using DAERS, sites should inform the Protocol Chairs and DAIDS Medical Officers, via email, as soon as the site is aware of the event.

7.4.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0, dated November 2014 will be used for this study. This table is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

Grading severity for adverse events will follow Table 6 below.

Table 6
Severity Grading of Events

Severity Grading of Events			
Grade 1 Mild	**Grade 2** Moderate	**Grade 3** Severe	**Grade 4** Potentially Life-Threatening
Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities OR resulting in hospitalization	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability or death

7.4.4 Expedited AE Reporting Period

The EAE reporting period begins at the time of enrollment and continues through the Week 48 Visit.

After the protocol-defined AE reporting period, unless otherwise noted, only suspected unexpected serious adverse reactions, as defined in Version 2.0 of the EAE Manual and assessed as related to the study counseling procedures, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8 PARTICIPANT SAFETY MANAGEMENT

8.1 Management of Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the counseling procedures, whether or not related to the counseling procedures.

All reportable adverse events identified in this study will be source documented consistent with the policies and procedures referenced in Section 10. Among other details, source documentation will include the severity of each event (graded as described in Section 7.4.3) and its relationship to study counseling procedures, assessed by the site investigator according to the following categories and definitions:

Related	There is a reasonable possibility that the adverse event may be related to the study counseling procedures
Not related	There is not a reasonable possibility that the adverse event may be related to the study counseling procedures

Acute management of any AE will be according to best clinical practices and the judgment of the site investigator in consultation with the psychiatrist involved with the participant's care. The relationship between the AE and the study counseling procedures will be presumed unless a clearly recognized etiology is identified.

This protocol studies depression treatment strategies in participants who have been prescribed certain medications by their primary physician or a consulting site prescribing clinician. Note that no drugs are supplied as part of this study. All drugs, including those being studied at non-standard doses, must be provided by participants' clinical care providers by prescription. Any abnormal laboratory results must be communicated promptly to the treating physician and site investigator. While these medications are not given as study drugs, they are concomitant medications, and they need to be managed per the Medical Management Algorithm on the COMB-R arm, or per standard of care in the ESC arm of the study.

Toxicities have been associated with medications used in the treatment of depression. In the COMB-R sites, toxicities will be managed by the site prescriber in conjunction with the Medication Management Manual (MM), package insert, clinical judgment, and consultation with the protocol investigators as needed. Similarly, ESC sites will manage toxicity as per standard of care, package insert, and best medical judgment. The protocol chairs will provide guidance on clinical management of any toxicities as needed.

8.2 Criteria for Premature Discontinuation of Study Participation

Participants must be discontinued from the study if:

- The site investigator, NIAID, IMPAACT, the Office for Human Research Protection (OHRP), other governmental agencies or the site's IRB discontinues this study;
- The participant/legal guardian refuses further participation in the study;
- The investigator determines further participation would be detrimental to the participant's health or well-being;
- The participant fails to comply with the study requirements, so as to cause harm to self or seriously interfere with the validity of the study results

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a multisite, two-arm cluster (site)-randomized trial of a Health and Wellness Cognitive Behavioral Therapy (H&W CBT) and Medication Management (MM; COMB-R) intervention for depression. Prior to the start of enrollment, all the selected sites will be randomized to either the COMB-R group or the Enhanced Standard of Care (ESC) group, and then each site will enroll participants and provide the intervention to which that site was randomized. The study population will be HIV-infected youth in the U.S., who are between 12 and 24 years old (inclusive), and who have been diagnosed with depression and have a QIDS-C score of $\geq$ 11. The primary objectives are to compare the two study arms with respect to depression outcomes, and biological measures of health after 24 weeks. The secondary objectives are to compare the two study arms with respect to adherence to HIV and depression treatment; examine whether differences in depression outcomes are maintained at 48 weeks; assess whether demographic, behavioral and biological factors could moderate the efficacy of COMB-R compared to ESC; assess whether COMB-R is associated with improved behavioral risk outcomes; describe the implementation fidelity at COMB-R sites and counseling strategies at ESC sites; compare the number of interim visits, the frequency of medication use, and acceptability of COMB-R and ESC among participants and clinicians; and compare the frequency and types of Grade 3 or higher adverse events, psychological hospitalizations and suicide attempts. The exploratory objectives will assess inflammatory biomarkers and their moderating effect on intervention outcomes.

It is anticipated that 14 sites will be randomized to either the COMB-R arm or the ESC arm. The target sample size will be to enroll 156 participants (to achieve 140 evaluable, allowing for up to 10% loss to follow-up; a participant is evaluable if QIDS-SR data at both baseline and week 24 were obtained). The sample size may be increased if the percentage of non-evaluable participants or the observed intracluster correlation coefficient is higher than assumed for sample size calculations (see Section 9.5.1 for details). Each site is expected to enroll a minimum of eight participants. Accrual is expected to require approximately two years. The expected study duration for each participant will be approximately 48 weeks.

Randomization of sites instead of individual participants was chosen because it would be difficult for the same provider to deliver ESC to some patients and COMB-R to other patients in the same clinic without any loss in fidelity of ESC or COMB-R or cross-talk between patients in the two study arms. It would be ideal to screen and enroll all participants in the study before the sites are randomized to ESC or COMB-R, to avoid selection bias (discussed below). However, this design was deemed not feasible, because it would not be possible to enroll a sufficient number of participants in a short enough period of time; based on the site implementation plans, the number of anticipated enrollments in the first six months of enrollment was three-five participants for nine sites, and more than seven participants for only two sites. Consequently, participants will be enrolled after the sites have been randomized.

One potential source of bias with this design is selection bias, which can occur if not all potentially eligible participants are approached for enrollment (e.g., if the COMB-R sites are more stringent in selecting potential participants to be approached). Selection bias is of much greater concern with this site-randomized design than in an individually randomized trial, because enrollment of participants after the site has been randomized means that the site randomization cannot protect against imbalance in participant characteristics between study arms. The sites will be randomized using a restricted randomization procedure designed to balance key characteristics of the site populations. In addition, the protocol includes several design features to minimize selection bias, including defining eligibility criteria that apply equally to both study arms; requiring sites to obtain screening numbers for all potentially eligible participants and randomizing the order in which the site can approach potential participants for enrollment; and collecting limited data on patients who do not enroll so that their characteristics can be compared to those of participants who did enroll, to assess the potential extent of selection bias.

9.2 Outcome Measures

9.2.1 Primary Outcome Measures

Depression Outcomes:

- QIDS-SR score at Week 24 (primary efficacy outcome)
- Response to Treatment, defined as a decrease in QIDS-SR score by >50% from entry to week 24
- Remission, defined as a QIDS-SR score $\leq$ 5 at week 24

Biological Measures:

- CD4 cell count at Week 24
- Plasma HIV RNA level at Week 24

9.2.2 Secondary Outcome Measures

- Adherence to anti-HIV medications and psychiatric medications at each assessment for the first 24 weeks (during active treatment) and at 48 weeks, as measured by self-report; and adherence to study visits and psychotherapy sessions
- Depression outcomes (QIDS-SR score, Response to Treatment, and Remission) over 48 weeks. Note: The following factors will be assessed as potential effect-modifiers (moderators): Demographic: age, gender. Behavioral: HIV acquisition category, initial level of depression. Biological: baseline CD4, nadir CD4, plasma HIV RNA, CDC category.
- Behavioral risk outcomes: alcohol/drug use, sex-risk behaviors at week 24 and week 48
- Implementation fidelity (COMB-R sites); counseling strategies and medication patterns (ESC sites) (see Section 5 for measures).

- Number of interim visits; frequency of medication use; acceptability among participants and clinicians (see Section 5 for measures).

- Grade 3 or higher adverse events, psychological hospitalizations, and suicide attempts

9.2.3 Exploratory Outcome Measures

- Plasma inflammatory biomarkers at 24 and 48 weeks

9.3 Randomization

Prior to the start of enrollment, all of the selected sites will be randomized to either the COMB-R group or the ESC group, and then each site will enroll participants and provide the intervention to which that site was randomized. The sites will be randomized using a restricted randomization procedure (61) to avoid imbalances in participant characteristics. A pre-study survey of the sites collected information on site characteristics, including number of youth served, route of HIV infection (perinatal versus behavioral), age (12-18 versus 19-24 years of age), and gender. Among the 14 sites selected to do IMPAACT 2002, four sites see primarily behaviorally HIV-infected youth, four other sites see large numbers of patients, and the other six sites appear to be approximately balanced with respect to route of infection and numbers of patients seen. Within the above groupings, the sites are well-balanced across gender and age. If two of the four primarily behavioral infection sites and two of the four large sites are randomly assigned to each study group, and three of the remaining six sites are randomly assigned to each study group, then the two groups would be expected to be approximately balanced with respect to number of youth served, route of HIV infection, age, and gender.

A computer program will be written to generate all possible allocations of the 14 sites that have two primarily behavioral sites in each study group and two large sites in each study group. To further protect against imbalance in gender, age, mode of transmission, severity of depression and viral load suppression status, the program will discard any allocations that exceed a maximum acceptable imbalance in any of these characteristics, and then will choose one allocation randomly from all of the allocations with acceptable balance. Specifically, before the randomization is performed, the sites will determine potentially eligible participants. Sites should consider youth, with or without a history of depression, with or without a history of mental health treatment, and those currently in mental health treatment; providing they are thought to meet study eligibility criteria. Sites will then be required to submit the following summary information for their potentially eligible patients: % <18 years vs. > 18 years, % male vs. female, % perinatal vs. behavioral HIV acquisition, % with moderate vs. severe depression based on clinician judgment, and % virally suppressed vs. not suppressed (below or not below the level of detection as defined by the laboratory). A maximum acceptable difference between the means of the site-specific proportions in the COMB-R and ESC arms will be specified (e.g., allowing the means to differ by no more than 0.25 standard deviations (SD) or no more than 10% (i.e. their ratio should be between 0.9 and 1.1)). The computer program will randomly choose one allocation from among all allocations of sites to arms that have less than or equal to the maximum difference for each of the five characteristics of interest. Imbalance criteria may be adjusted (for example, allowing the means to differ by no more than 20% instead of 10%) if they result in too few possible allocations.

Initially, there will not be any limits on enrollment according to the above characteristics. During enrollment, the core protocol team will monitor the balance of the above characteristics between arms quarterly or as needed (blinded to which arm is which), and if an imbalance greater than the maximum allowable imbalance is identified, will impose enrollment limits in the DMC enrollment system for all sites in one arm or the other to force subsequent enrollments to be from a specific category of age (<18 years or > 18 years) or, gender (male or female) or HIV acquisition route (perinatal or behavioral) or depression level (moderate or severe) or viral suppression (suppressed or not suppressed), as needed, to achieve approximate balance of these characteristics in the two study arms.

Potentially eligible patients will be screened as described in Section 4.4. All participants at ESC sites will be directly assigned to ESC and all participants at COMB-R sites will be directly assigned to COMB-R.

9.4 Sample Size and Accrual

9.4.1 Sample Size

The proposed sample size for IMPAACT 2002 is approximately 140 evaluable participants (an average of 10 evaluable participants per site) to be enrolled at 14 clinical research sites. A total of 156 participants will be enrolled to allow for up to 10% loss to follow-up by week 24 (note: the team anticipates that there may be higher loss to follow up after week 24, but no more than 15% total through week 48). Should the percentage of participants who are non-evaluable at Week 24 exceed 10%, the sample size may be increased to achieve 140 evaluable (see Section 9.5.1 for details). This sample size was chosen to provide high power to detect a clinically important difference in the primary efficacy outcome measure, the QIDS-SR score between study arms at 24 weeks. The QIDS-SR is a 16-item scale assessing nine depressive symptoms. Total QIDS-SR scores range from 0-27. QIDS-SR scores of six-ten reflect mild symptoms, 11-15 reflect moderate symptoms, and $\geq$16 reflect severe symptoms. The study team indicated that the smallest clinically important difference to detect would be a difference in the QIDS-SR score of 0.8 standard deviation (SD) units, which corresponds to a difference of about three to four points on the QIDS-SR scale based on the observed standard deviations at baseline in the ATN 080 study. Note that an effect size of 0.8 SD is plausible and conservative in that the effect size observed at Week 24 in the ATN 080 study of this intervention was almost two times larger.

IMPAACT 2002 is a cluster-randomized trial where each cluster is a clinical research site. The statistical power to detect a difference between arms depends on the number of clusters (sites) per arm (n), the average number of participants per site (m), and the intra-cluster correlation coefficient (ICC) (61). The ICC is a measure of within-cluster (within-site) correlation and is defined as ICC= (between-cluster variation)/(between-cluster variation + within-cluster variation). An ICC of zero indicates that the within- cluster variation outweighs the between-cluster variation to the extreme, so that essentially there is no within-cluster correlation. In contrast, an ICC of 1 indicates perfect within-cluster correlation (0 within-cluster variation). In this case, the sample devolves into the number of clusters.

For cluster-randomized trials with relatively small numbers of clusters (fewer than 15-20 clusters per treatment arm), the recommended analysis approach (61) is a cluster-level analysis, in which a summary outcome measure is calculated for each cluster (e.g., the mean score or response proportion across participants in that cluster) and the cluster-specific outcome measures are compared between treatment arms using an appropriate two-sample test such as a t-test.

Cluster-randomized trials typically require larger sample sizes than individual-randomized trials, because cluster randomization provides less precise (more variable) estimates of treatment effects due to the between-cluster variation. The design effect (DE) is the multiplier that indicates the increase in sample size needed to achieve a given power compared to the sample size that would be required if there were no cluster randomization ($SampleSize_{RT}$):

$DE= 1 + (m-1)*ICC$

The final sample size for the cluster randomized trial ($SampleSize_{CRT}$) is:

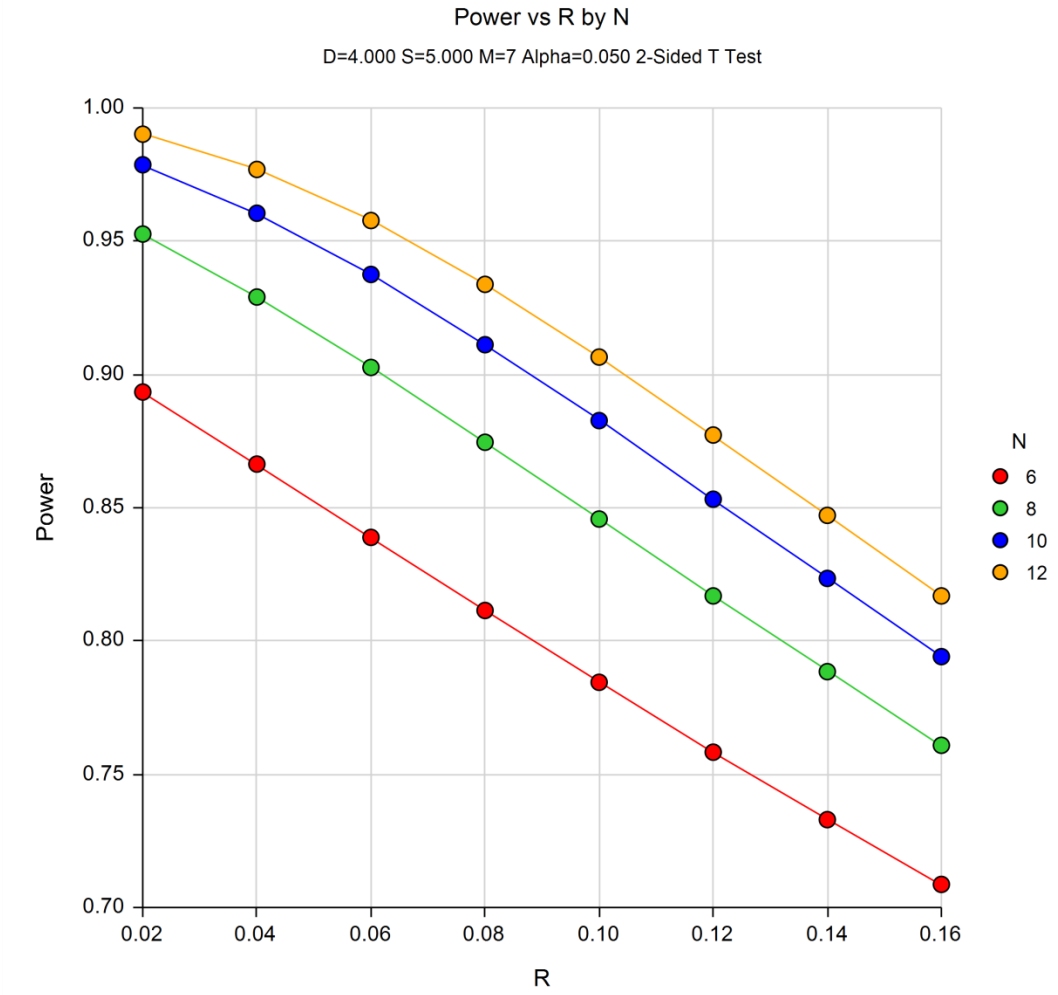
$SampleSize_{CRT} = SampleSize_{RT} * DE = SampleSizeRT * (1 + (m-1)*ICC)$

An estimate of the ICC is needed for sample size calculations. The ATN 080 study was too small to provide ICC estimates (only four sites were randomized) and a literature search did not identify any ICC estimates for the QIDS-SR. The University of Aberdeen Health Services Research Unit has compiled a database of ICCs calculated from a number of different interventions and settings in cluster randomized studies of interventions to change physician practices (62). In this database, the pre-intervention ICCs for the SF36 Mental Health Component score in cluster-randomized trials which randomized at the practice level ranged between 0.02 and 0.05 in patients with different diseases (benign prostatic hyperplasia, microscopic haematuria, asthma, angina, and epilepsy). Also, in a cluster randomized trial of class-room cognitive–behavioral therapy to reduce depression symptoms in high-risk adolescents, the estimated ICC for the Short Mood and Feelings Questionnaire (SMFQ) was 0.025 in the pilot phase and the ICCs (upper 95% confidence limit) were as follows in the main trial: baseline < 0.001 (0.006); 6 months 0.007 (0.026); 12 months 0.012 (0.039). Based on the above ICC estimates, the ICC is anticipated to be in the range 0.02-0.05, but to be conservative, a range of 0.02-0.16 was used for sample size calculations. As described in Section 9.5.1, an interim analysis will be performed to estimate the ICC using the baseline data, to assess whether the sample size should be increased to increase power.

Sample size calculations were performed using the cluster randomization modules in the PASS 11 software. The sample size was chosen to provide high power to detect a clinically important difference in the primary efficacy outcome measure, the QIDS-SR score between study arms at 24 weeks. For the secondary efficacy outcome measures (treatment response, remission, CD4, and viral suppression), the effect size that would be detectable with 80% power with the chosen sample size was calculated. No adjustment for multiple comparisons was made in the sample size because the week 24 QIDS-SR score has been designated as the primary efficacy outcome; however, the interpretation of the results will comment on whether a multiple comparisons adjustment would change the conclusions of the analyses for the efficacy outcomes. Sample size calculations for comparison of means used the t-test and for comparisons of proportions used the two-sided Z test (unpooled).

Figure 1 shows the power to detect a difference in means of 0.8 SD units in QIDS-SR score (e.g., a difference of four points if the standard deviation is 5) with seven sites per arm and a range of ICCs (R) and average number of evaluable participants per site (N), using a two-sided 0.05 significance level. With an average of ten evaluable participants per site (N=10), the study will have at least 90% power if the ICC is less than 0.09 and at least 80% power if the ICC is between 0.09 and 0.15.

Figure 1: Power to detect 0.8 SD difference in means (D) in QIDS-SR score at 24 weeks with seven sites per arm and a range of ICCs (R) and average number of evaluable participants per site (N), using a two-sided 0.05 significance level.



In ATN 080, the treatment response proportion in the control group was 20% and the remission rate was 10%, which are unusually low. The study team anticipates that the rates in the ESC group will be 50% better than in the ATN 080 control group, namely 30% and 15%, respectively. Figure 2 shows the response probability in the COMB-R group (P1.1) that would be detectable with 80% power if the response probability in the ESC group is 30%, for a range of ICC values and average numbers of evaluable participants per site (M1), using a two-sided 0.05 significance level. With an average of 10 evaluable participants per site, the study would be able to detect an increase in treatment response from 30% to 55-60% (a 25-30% absolute increase) if the ICC is in the range 0.02-.08, and an increase from 30% to 60-65% (a 30-35% absolute increase) if the ICC is in the range 0.08-0.15. Figure 3 shows the remission probability in the COMB-R group (P1.1) that would be detectable with 80% power if the remission probability in the ESC group is 15%, for a range of ICC values and average numbers of evaluable participants per site (M1), using a two-sided 0.05 significance level. With an average of 10 evaluable participants per site, the study would be able to detect an increase in remission from 15% to 37-42% (a 22-27% absolute

increase) if the ICC is in the range 0.02-.08, and an increase from 15% to 42-47% (a 27-32% absolute increase) if the ICC is in the range 0.08-0.15.

Figure 2: Response probability in the COMB-R group (P1.1) that would be detectable with 80% power if the response probability in the ESC group (P2) is 30% for a range of ICC values and average numbers of evaluable participants per site (M1), using a two-sided 0.05 significance level

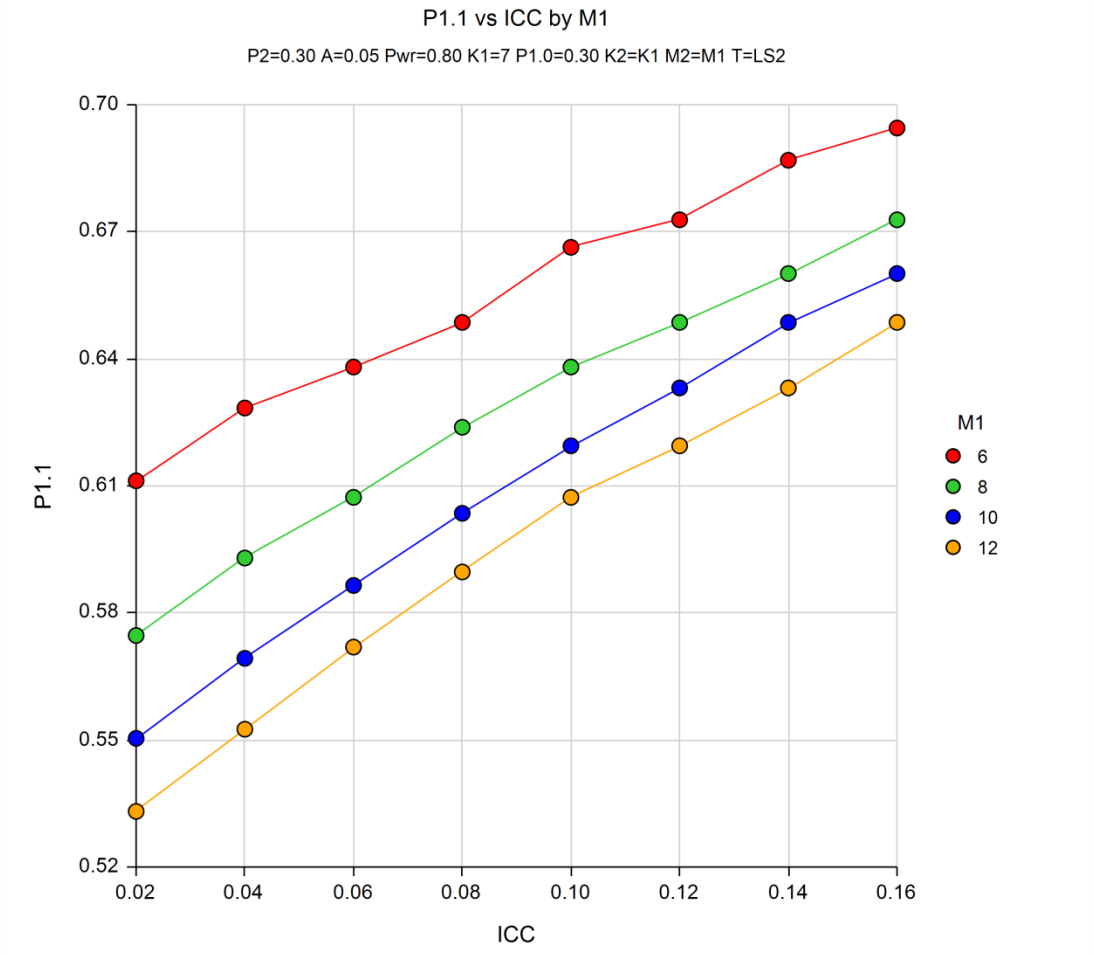
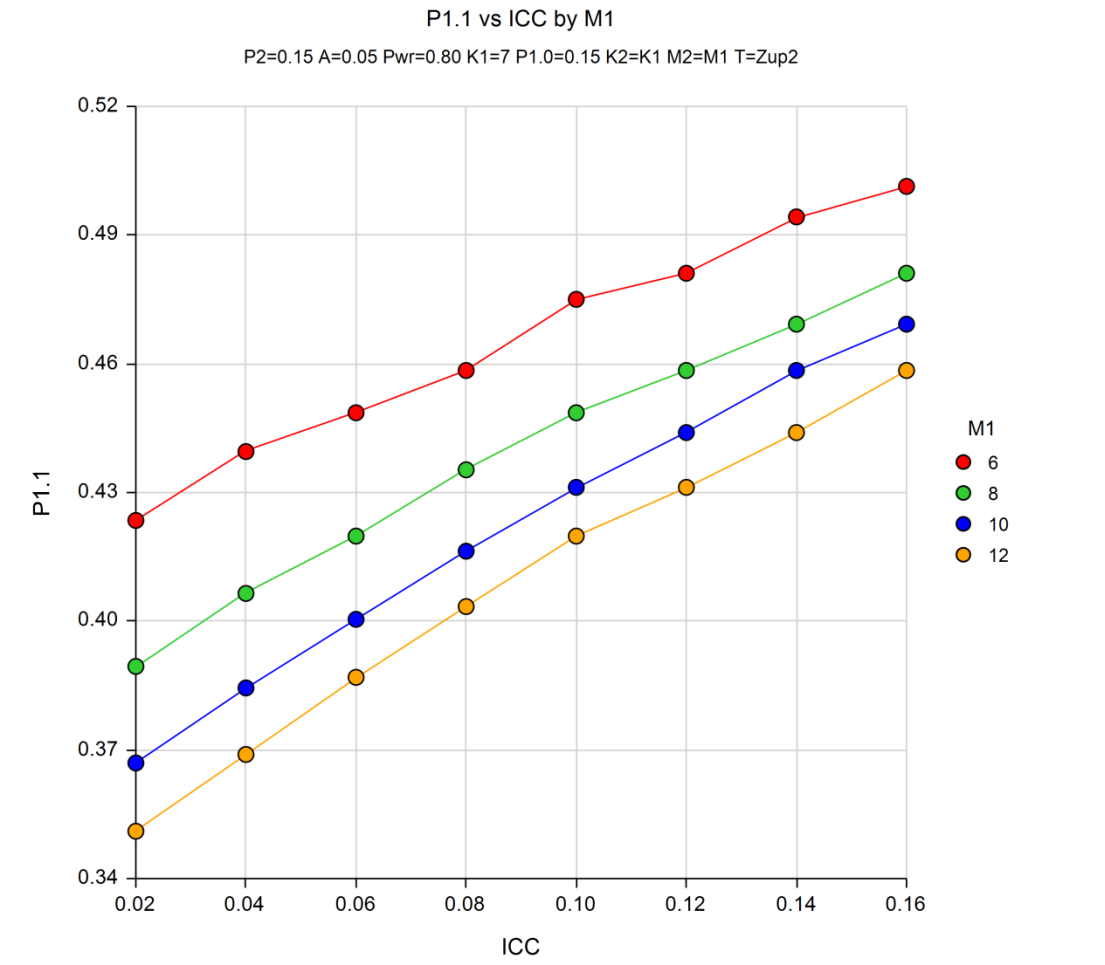
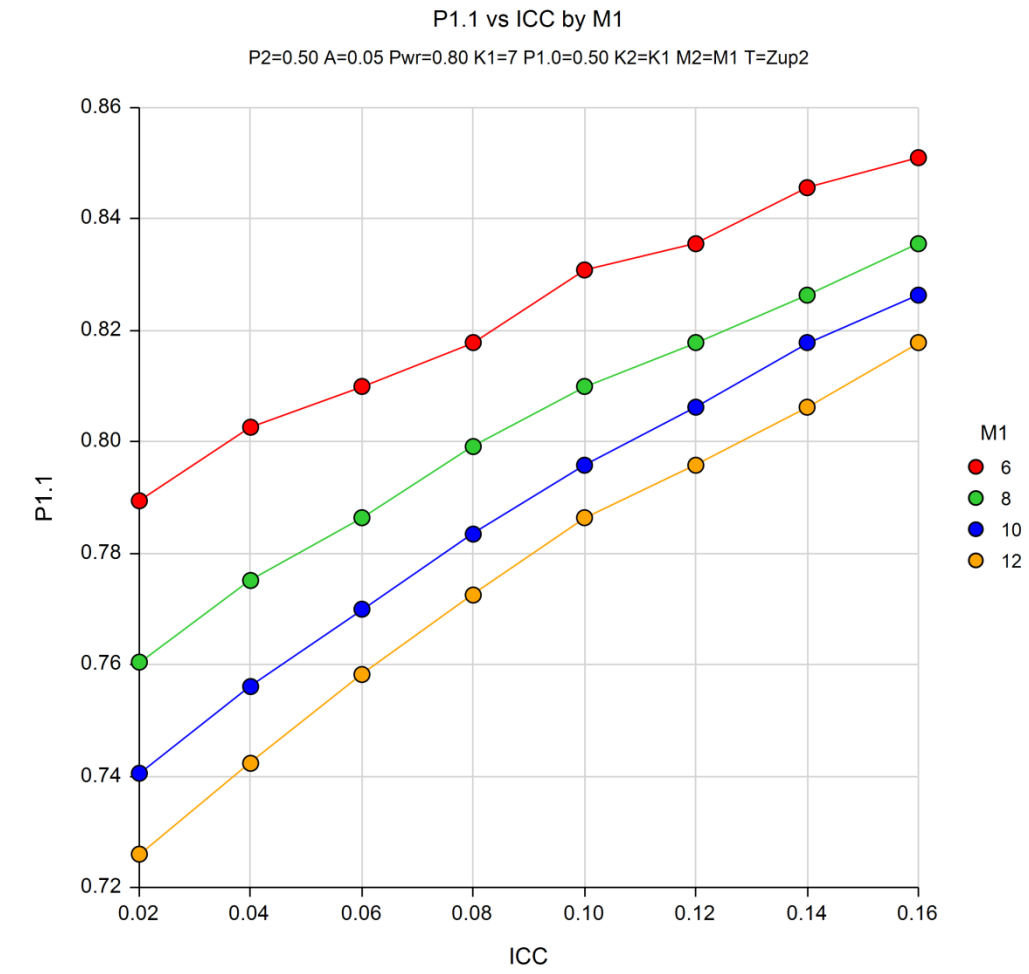


Figure 3: Remission probability in the COMB-R group (P1.1) that would be detectable with 80% power if the remission probability in the ESC group (P2) is 15%, for a range of ICC values and average numbers of evaluable participants per site (M1), using a two-sided 0.05 significance level.



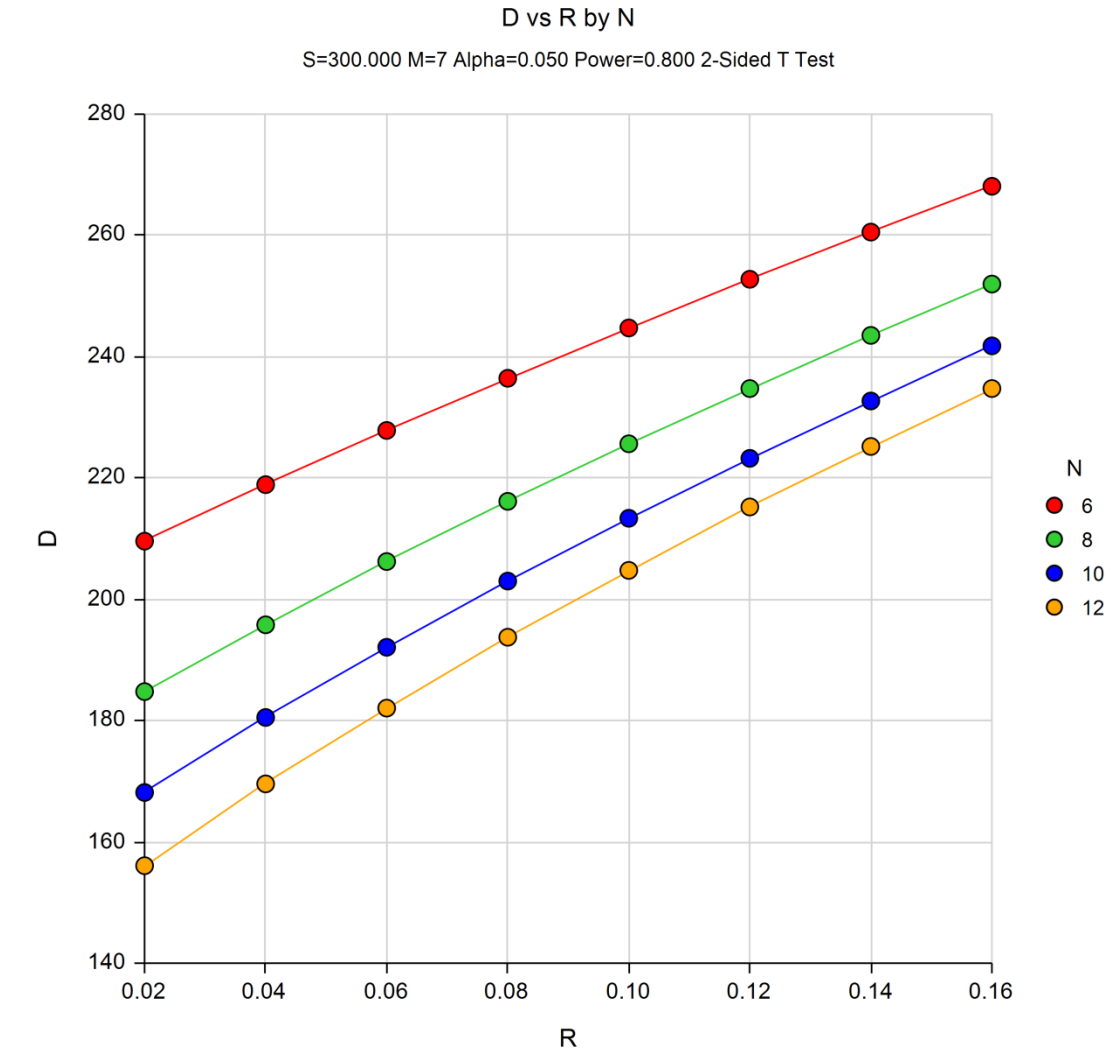
In ATN 080, 50% of participants had baseline viral load <400 copies/mL. Figure 4 shows the viral suppression probability in the COMB-R group (P1.1) that would be detectable with 80% power if the viral suppression probability in the ESC group is 50%, for a range of ICC values and average numbers of evaluable participants per site (M1), using a two-sided 0.05 significance level. With an average of 10 evaluable participants per site, the study would be able to detect an increase in viral suppression from 50% to 74%-78% (a 24-28% absolute increase) if the ICC is in the range 0.02-.08, and an increase from 50% to 78%-82% (a 28-32% absolute increase) if the ICC is in the range 0.08-0.15.

Figure 4: Viral suppression probability in the COMB-R group (P1.1) that would be detectable with 80% power if the viral suppression probability in the ESC group (P2) is 50%, for a range of ICC values and average numbers of evaluable participants per site (M1), using a two-sided 0.05 significance level.



In ATN 080, the mean CD4+ cell count was approximately 500 cells/mm^3 and the standard deviation was approximately 300 cells/mm^3. Figure 5 shows the difference in mean CD4+ cell counts (D) that would be detectable with 80% power if the ESC group had the same mean and SD as in ATN 080, for a range of ICC values and average numbers of evaluable participants per site (N), using a two-sided 0.05 significance level. With an average of 10 evaluable participants per site, the study would be able to detect a difference of 165-205 cells/mm^3 if the ICC is in the range 0.02-.08, and a difference of 205-235 cells/mm^3 if the ICC is in the range 0.08-0.15.

Figure 5: Difference in Mean CD4+ Cell Count Detectible (D) with 80% Power if the ESC group has mean 500 cells/ mm^3 and SD 300 cells/mm^3, for a range of ICC values (R) and average numbers of evaluable participants per site (N), using a two-sided 0.05 significance level.



9.4.2 Accrual

Accrual of the target sample size of approximately 156 participants (140 evaluable) is expected to be completed within 24 months of when accrual opens at each site. There will be a cap of at most ten participants enrolled at any single site in the first year of accrual, and the study team will re-evaluate whether to have a cap for the second year of accrual.

9.5 Monitoring

This study will be monitored at multiple levels, consistent with standard IMPAACT procedures. A study monitoring plan that details monitoring roles and responsibilities and data to be reviewed

at each level will be prepared before the study opens to accrual. The core protocol team (which consists of the protocol chair, vice-chairs, medical officers, statisticians, data managers, and clinical trial specialists) is responsible for closely monitoring study progress, including timely achievement of key milestones, the quality of study conduct, and safety. IMPAACT leadership will also monitor study progress and quality. The IMPAACT Study Monitoring Committee (SMC) will also conduct formal reviews of study conduct and safety. Unless otherwise specified, monitoring reports distributed to the protocol team will be pooled across the COMB-R and ESC arms. Monitoring reports distributed to the SMC may be broken out by blinded study arm. In addition, an interim analysis to confirm assumptions made in the power analysis will be performed as noted in Section 9.5.1

Please refer to Section 7.0 for more information on safety assessment and reporting and Sections 10.0 and 11.0 for more information on on-site monitoring and quality management at the site level. Further information on monitoring of study progress, quality of study conduct, and participant safety across sites is provided below.

9.5.1 Monitoring of Study Accrual and Retention

The study team anticipates that accrual of the target sample size of 156 participants (140 evaluable) will require approximately 24 months and expects a minimum of eight participants to enroll in each site, with a minimum of three enrollments in the first six months. The protocol team will monitor the timing of site-specific study activation, which will determine when each site will begin accruing participants, and accrual performance following activation. The protocol team will closely monitor participant screening, accrual and retention based on reports that will be generated by the SDMC monthly during accrual and every three months once accrual is complete. The protocol team may decide to revise this schedule as needed. Using these reports, the protocol team will monitor accrual closely, relative to the study-specific accrual plan that has been established in collaboration with the study sites. Additionally, the protocol team will monitor pre-screening and recruitment activities across all sites during study implementation. The team will specifically monitor the enrollment of eligible participants at each site (including reasons for lack of enrollment). To monitor for selection bias, the characteristics (gender, age, mode of transmission, severity of depression and viral load suppression status) of those participants screening but not enrolling will be compared between study arms. The same characteristics will be compared overall and within treatment arms for those participants enrolling vs. not enrolling into the study. In the event that accrual or retention rates fall below target team members will work with study sites to identify operational issues or problems, and take appropriate action to address those issues. Monitoring of imbalance in baseline characteristics between the COMB-R and ESC arms is described in Section 9.3.

The core protocol team will also monitor the percentage of evaluable participants, namely those with both baseline and Week 24 QIDS-SR data, as participants reach the Week 24 visit. Should the percentage of participants who are non-evaluable at Week 24 exceed 10%, the sample size may be increased to achieve 140 evaluable. Additionally, the numbers and characteristics (gender, age, mode of transmission, severity of depression and viral load suppression status) of non-evaluable participants will be compared between study arms. Characteristics of those evaluable vs. non-evaluable will also be compared overall and within treatment arms.

To check the validity of the assumptions used for sample size calculations, an interim analysis will use the baseline QIDS-SR data to estimate the ICC. This interim analysis will be performed either (a) once at least 5 participants at each site have completed Week 0 or (b) 18 months from

the start of study accrual, whichever occurs first. If the estimated ICC is larger than 0.15 (the largest value for which the selected sample size provides 80% power), the protocol team will assess whether to increase the number of participants to be enrolled, to ensure adequate statistical power for the primary study objective.

IMPAACT leadership will also monitor accrual relative to the study accrual plan and retention, based on standard IMPAACT study accrual and retention reports that they receive on a monthly basis. The SMC may be asked to evaluate accrual as part of a review, and, if so, it will report its findings and recommendations to the study team and IMPAACT leadership. IMPAACT leadership, including the SMC, may request action plans from the team to address accrual delays and/or shortfalls and will monitor the implementation and outcomes of such plans as part of an overall assessment of the feasibility of the study to achieve its objectives.

9.5.2 Monitoring of Study Conduct

Core protocol team members will review key indicators of the quality of study conduct based on reports generated periodically by the SDMC and take action with study sites as needed to ensure high quality study conduct throughout the period of study implementation. These reports will include information on the quality and completeness of data collection, visit completeness, and the fidelity of implementation of the study intervention (medication management report and CBT adherence checklist – see Section 5.4).

9.5.3 Monitoring of Participant Safety

Participant safety will be closely monitored by the core protocol team through periodic reviews of adverse event reports (pooled across the COMB-R and ESC arms) generated by the SDMC. These reports will provide summaries of ≥ Grade 3 adverse events, psychological hospitalizations, and suicide attempts. At the time of each review, the DAIDS Medical Officer will also review any EAEs (defined in Section 7.3) reported to the DAIDS Safety Office that are not yet reflected in the data reports. Core team members will continually evaluate the pattern and frequency of reported adverse events and assess for any individual occurrences or trends of concern. Relationship status of adverse events to COMB-R or ESC counseling will also be summarized.

9.5.4 Study Monitoring Committee

An independent IMPAACT SMC will also review this study regularly with respect to study progress, quality of study implementation, and conduct (including retention and data completeness), and safety. No interim efficacy analyses are planned because the entire sample size will be required to assess the efficacy of the intervention. Reviews will be scheduled at least annually. The SMC will review the same type of data reports as the core protocol team; however, data may be provided to the SMC by blinded study group. Based on any of its reviews, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide specific operational recommendations to help address any study implementation challenges that may be identified during their reviews.

9.6 Analyses

This section provides a brief overview of the data analyses to address the objectives of the study. A comprehensive statistical analysis plan with full details of the planned analyses will be developed at least six months prior to the first SMC review of safety data.

9.6.1 Primary Objectives

The primary analyses to address the primary objectives will be cluster-level analyses, where the unit of analysis is the site; although this method does not use all the information in the data, this method is recommended when there are fewer than 15-20 clusters per group, because individual-level analyses do not appear to perform robustly with small numbers of clusters (61). The cluster-level analyses will involve a two-stage procedure. The first stage will calculate a summary measure for each site – the mean for continuous outcome measures (QIDS-SR, CD4 count) and the proportion for dichotomous outcomes (response to treatment, remission, undetectable plasma HIV RNA). The second stage will perform a two-sample t-test (with two-sided alpha =0.05) on the site-specific summary measures. Note that the alpha level will not be adjusted for multiple comparisons, because the Week 24 QIDS-SR score has been designated as the primary efficacy outcome and the response, remission, CD4, and RNA outcomes are considered secondary efficacy outcomes; however, the interpretation of the results will comment on whether a multiple comparisons adjustment would change the conclusions. If the summary measures have a skewed distribution, a log transformation will be performed before doing the t-test. Methods based on the t-test have been shown to be highly robust to departures from the underlying assumptions. However, with small numbers of clusters per arm, the cluster-level t-test will be less robust to non-normality of the underlying distribution of cluster summaries, and it will be difficult to make a reliable assessment of non-normality. A non-parametric test that does not rely on a normality assumption, but which may be less powerful than the t-test, such as the Wilcoxon rank sum test or a permutation test (based on all the permissible allocations that were generated for the site randomization) will be performed to supplement the primary analysis.

The primary analysis will focus on the primary outcome measures at Week 24 that are listed in Section 9.2.1, because the protocol team believes that it is important that the intervention demonstrate a lasting effect; a shorter term effect may not be as clinically meaningful. Secondary analyses that use information from earlier time points will also be conducted to supplement the results of the primary analyses, including analyses of the change in outcome measures over time (such as cross-sectional summaries at each time point, with the non-parametric Wei-Johnson test for change over time between groups). As noted above, cluster-level analyses are robust to departures from assumptions, but do not use all the information in the data, since the outcomes are measured at the individual participant level. Secondary analyses of the primary outcome measures will be conducted using individual-level regression methods, including mixed-effects linear regression models for continuous outcomes and generalized estimating equations (GEE) models for dichotomous outcomes, to supplement the primary cluster-level analyses. For example, linear mixed models will be used to evaluate the influence of the COMB-R condition on QIDS-SR trajectories over the four assessment points.

Descriptive analyses of participant characteristics at study entry and Week 24 (gender, age, mode of transmission, severity of depression, CD4 and RNA levels and viral suppression status) will be performed using appropriate statistical tests for categorical and continuous measures of clustered data as noted above. To assess the potential for selection bias, the numbers and characteristics

(gender, age, mode of transmission, severity of depression, and viral suppression status) of participants screening but not enrolling in the study will also be compared between treatment groups, and the characteristics of participants enrolling vs. not enrolling will be compared overall and within treatment arms as well. We will also compare patient characteristics according to treatment arm and whether or not sites allowed parental waivers of consents.

High rates of loss to follow-up before Week 24, particularly if differential between randomized arms might affect the ability of the study to answer its primary objective, i.e. power may be reduced and the interpretation of any difference between randomized arms may be complicated by potential differences between participants who do versus do not remain in follow-up, particularly if this also differs between randomized arms. Allowance for a loss to follow-up rate of up to 10% prior to Week 24 has been built into the sample size/power considerations for the study, and the protocol (Schema and Section 9.5.1) specifies that the sample size may be increased if the loss-to-follow-up rate exceeds 10%.

If more than 10% of participants are lost to follow-up before Week 24, or if a larger proportion of participants are lost to follow up in one arm (especially if the loss is due to serious adverse events, or suicide attempts), several analyses will be undertaken to explore the potential effects of missing data on the conclusions of the study, The characteristics at study entry (gender, age, mode of transmission, severity of depression and viral load suppression status) for participants who discontinued from the study before Week 24 will be compared between treatment arms. Characteristics of participants discontinuing vs. not discontinuing before Week 24 will also be compared overall and within treatment arms. In addition, the reasons for losses to follow-up will be assessed and compared between treatment arms, with special attention paid to reasons related to Grade 3 or higher adverse events, psychological hospitalizations and suicide attempts. Descriptive comparisons by site will be performed for sites with sufficient numbers of participants. In addition, the probability and timing of loss to follow-up will be summarized and compared using Kaplan-Meier plots and the log-rank test.

Sensitivity analyses will be conducted to explore the potential impact of missing data on the conclusions of the primary efficacy analyses. Of primary concern are missing QIDS-SR scores at Week 24 for participants who had low or decreasing QIDS-SR scores at time points before Week 24. The sensitivity analyses will be done in two ways: (a) as an extreme, by imputing missing QIDS-SR scores at Week 24 so as to minimize the difference between randomized groups (e.g., if the primary efficacy analysis among participants with available Week 24 QIDS-SR score suggests that COMB-R is better than ESC, impute a high Week 24 QIDS-SR score for COMB-R participants who do not have a Week 24 QIDS-SR score, and impute a low Week 24 QIDS-SR score for ESC participants who do not have a Week 24 QIDS-SR score, and (b) more plausibly, by imputing missing QIDS-SR scores at Week 24 as the mean of the Week 24 QIDS-SR scores for participants who had that evaluation and also had similar QIDS-SR scores at earlier time points. Use of multiple imputation procedures will be considered if the attrition rate is high. The interpretation will need to be more cautious if the results of these analyses suggest different conclusions.

9.6.2 Secondary and Exploratory Objectives

Adherence to both HIV and depression medication and depression counseling sessions will be assessed as continuous and categorical measures. For example, adherence to HIV medications will be dichotomized based on the data distribution of the number of days when doses were missed. Likert scales for self-reports of adherence frequency (how often did you take your medications the way you were supposed to?) and efficacy (how good a job did you do at taking

your medications?) will be dichotomized or analyzed as an ordinal measure, based on the observed data distribution. The proportions of expected counseling sessions attended will likewise be summarized and analyzed as a continuous or categorical measure based on the distribution observed. For each dichotomized adherence assessment, the proportions of participants with good versus poor adherence will be compared using the cluster-randomized methods described above. Similarly, if it is decided that the proportions of expected sessions can be analyzed as a continuous variable, methods noted above will be used to compare the COMB-R group to the ESC group at Week 24 and Week 48. A limitation of the depression medication adherence analyses is that adherence data will only be available for participants who are taking depression medications, so this will be a non-randomized comparison.

Week 48 depression treatment outcomes will be analyzed similarly to the Week 24 outcomes in order to ascertain whether any reported effects are maintained.

Analyses to adjust for imbalance and potential confounding, and assess effect modification will be performed using cluster-level methods and also using individual level regression methods (because cluster-level methods do not use all the information in the data). Each approach is described in turn below.

In the cluster-level analyses, adjustment for baseline covariates (e.g., the QIDS-SR score at entry) will be done by modifying the first stage of analysis and then completing the second stage. In the first stage, an individual-level regression of the individual outcome measures (e.g., QIDS-SR scores at Week 24) on the baseline covariates will be performed, ignoring the clustering of the data, and then the residuals between observed and predicted values from this model will be used as the summary measures in the second stage.

Specifically, in the first stage of the cluster-level analyses, all variables of interest except for the study group (ESC or COMB-R) will be entered into the regression model, and the summary statistic for each cluster will be the residual based on comparison of the summary measure calculated from the observed values of the outcome measure in that cluster and the summary outcome measure calculated from the predicted values of the outcome measures from the model in the absence of an intervention effect. For example, the site-specific residual for the QIDS-SR score at Week 24 will be the difference between the observed site-specific mean QIDS-SR score and the predicted site-specific mean QIDS-SR score (mean of the predicted QIDS-SR scores for that site from a linear regression model of Week 24 QIDS-SR score on baseline QIDS-SR score); the site-specific residual for the response proportion will be the difference between the observed site-specific response proportion and the predicted site-specific response proportion (predicted response proportion for that site from a logistic regression model). Then, in the second stage, these site-specific residuals will be compared using the two-sample t-test or other test as described above. Analyses of effect modification for cluster-level covariates and individual level covariates will be performed using methods described by Hayes and Moulton (56).

As noted above, cluster-level analyses are robust to departures from assumptions, but do not use all the information in the data, since the outcomes are measured at the individual participant level. Additional analyses will be conducted using individual-level regression methods, including mixed-effects linear regression models for continuous outcomes and generalized estimating equations (GEE) models for dichotomous outcomes, to supplement the primary cluster-level analyses. These individual level analyses will facilitate adjustment for baseline covariates, longitudinal analyses of the outcome measures over the 48-week study period, and assessment of effect modification by individual-level covariates. For example, linear mixed models will be used

to evaluate the influence of the COMB-R condition on QIDS-SR trajectories over the five assessment points.

If depression decreases over the course of treatment, we would expect the level of high risk sex and alcohol/drug behaviors to decline. We will assess whether COMB-R treatment for depression is associated with reduced alcohol/drug and sex risk behaviors using similar methods as described for the primary study objectives. Dichotomized measures for levels of high risk behaviors at weeks 24 and 48 will be compared between the COMB-R and ESC arms.

The implementation fidelity at COMB-R sites and the counseling strategies and medication patterns at ESC sites will be summarized using descriptive statistics. The use of medication, the number of therapy visits, and treatment acceptability, for both clinicians and participants will be described and compared for both COMB-R and ESC using standard descriptive statistics such as Chi square tests for categorical variables (such as clinician satisfaction rating items) and t-tests or non-parametric Wilcoxon rank sum tests for continuous measures (e.g., number of therapy sessions; client satisfaction score). CBT adherence checklist and ESC therapy checklist results as well as the COMB-R MM checklist will also be summarized.

The frequency and pattern of Grade 3 or higher adverse events, psychological hospitalizations and suicide attempts will be described for both treatment arms and the proportion of participants with each of these outcomes will be compared between arms using methods described for the primary study outcomes. Presumed relationship of adverse events to COMB-R and ESC counseling will be summarized and compared.

Similar methods to those described for the primary and secondary study objectives will be used to assess whether inflammatory markers decrease with the COMB-R intervention compared to ESC and whether the inflammatory markers could moderate the treatment effects on the primary outcome measures.

10 DATA HANDLING AND RECORD KEEPING

10.1 Data Management Responsibilities

As described in Section 4.4, data on screening and enrollment in this study will be collected using the DMC Subject Enrollment System.

Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled participants, including CRFs and supporting source data. In maintaining these records, sites must comply with the standards of source documentation specified in the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available on the web site referenced in Section 10.2).

CRFs are completed by site staff and, following quality control and quality assurance reviews, are keyed using a remote data entry system designated by the DMC, and transferred electronically to the DMC. Selected laboratory data are transferred electronically to the DMC through the Laboratory Data Management System (LDMS).

At the DMC, computerized checks are applied to the transferred data and, when required, data queries are issued for resolution by site staff. All data must be transferred to the DMC within timeframes specified in the forms instructions; queries must also be resolved in a timely manner.

Further information on the study CRFs and IMPAACT data management procedures, including a Forms Manual: Policies and Procedures for Forms Completion for DAIDS-Sponsored Clinical Trials, a comprehensive Computing Manual, and a User Manual for the Subject Enrollment System, is available on the DMC portal at www.fstrf.org.

10.2 Essential and Source Documents and Access to Source Data

All DAIDS policies referenced in this section are available at:
www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/ClinicalSite.aspx

Study sites must comply with the DAIDS policies on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials and Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. In its policy on Requirements for Manual of Operational Procedures, DAIDS requires sites to establish SOPs for maintaining essential and source documents in compliance with these policies. Site SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study, and site SOPs should be followed throughout the conduct of the study.

Per the DAIDS policy on Storage and Retention of Clinical Research Records, study records must be stored in a manner that ensures privacy, confidentiality, security, and accessibility during the conduct of the study and after the study is completed. Records must be retained for a minimum of three years after the completion of the study.

All study records must be accessible for inspection, monitoring, and/or auditing during and after the conduct of the study by authorized representatives of the study sponsors and their contracted monitors, IMPAACT, site IRBs/ECs, OHRP, and other applicable regulatory entities. Records must be kept on-site throughout the period of study implementation; thereafter, instructions for off-site storage may be provided by NIAID or NICHD. No study records may be removed to an off-site location or destroyed prior to receiving approval from NIAID or NICHD.

10.3 Quality Control and Quality Assurance

All study sites will conduct quality control and quality assurance procedures in accordance with current NIAID policies.
(http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/qmppolicy.pdf)

11 CLINICAL SITE MONITORING

Site monitors under contract to NIAID or NICHD will visit study sites to inspect study facilities and review participant study records including consent forms, CRFs, medical records, and laboratory records, to ensure protection of study participants, compliance with the IRB/EC approved protocol, and accuracy and completeness of records. The monitors will also review site essential document files to ensure compliance with all applicable regulatory requirements. Site

investigators and their designees will make study facilities and documents available for inspection by the monitors.

12 HUMAN SUBJECTS PROTECTIONS

12.1 Institutional Review Board/Ethics Committee Review and Approval

Each participating institution is responsible for assuring that this protocol, the associated site-specific informed consent forms, and study-related documents (such as participation education materials) are reviewed by an IRB/EC responsible for oversight of research conducted at the study site. Any amendments to the protocol must be approved by the responsible IRBs/ECs prior to implementation.

Subsequent to the initial review and approval, in accordance with 45 CFR 46.109(e), the responsible IRBs/ECs must review the study at least annually. Sites will submit documentation of continuing review to the DAIDS Protocol Registration Office in accordance with the DAIDS Protocol Registration Policy and Procedures Manual.

12.2 Vulnerable Participants

Study sites must comply with the requirements of the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research, which is available at: www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/ClinicalSite.aspx

The children enrolled in this study are considered vulnerable participants per 45 CFR 46 Subpart D. Site IRBs/ECs must consider the potential benefits, risks, and discomforts of the study to children and assess the justification for their inclusion in the study. As part of this assessment, IRBs/ECs must determine the level of risk to children in the categories specified in 45 CFR 46.404-407. Documentation of this determination is required to complete the DAIDS protocol registration process described in Section 13.2.

The risk category assigned by the IRB/EC determines whether parental/guardian permission is required, and if so, the informed consent requirements for the study at each site. Per 45 CFR 46.408 (b), the IRB/EC may find that the permission of one parent is sufficient for research to be conducted under 46.404 or 46.405. Where research is covered by 46.406 or 46.407, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child (as determined locally). Alternatively, IRBs/ECs may allow sites to obtain a waiver for parental permission per 45 CFR 46.408 (c), given the perceived minimal risk and potential benefit to participants. IRBs/ECs must document their risk determination and study sites should adapt the signature pages of their site-specific informed consent forms as needed to accommodate the parental consent requirements, if needed, associated with the IRB/EC determination.

12.3 Informed Consent

Written informed assent/consent must be obtained from a participant prior to performance of screening and enrollment procedures. If required per site IRB/EC, written permission may also be required from the participant's parent or legal guardian. A participant at a site that requires parental/guardian permission may enroll in the study as a minor, but reach the legal age of

consent during study follow-up. In this case, they will sign the assent form upon screening and will later sign the consent form once they reach legal age, at their next scheduled visit. A participant at a site that obtained a waiver for parental permission, may enroll in the study as a minor and sign the participant informed consent form without a separate parental consent.

The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Informed consent for specimen storage and future testing will be documented in the consent form; however, a participant (or parent/guardian if applicable) may still enroll in the study without agreeing to the storage and future testing of laboratory specimens. A copy of the consent form will be given to the participant (or parent or legal guardian).

Should the parent(s) of an enrolled participant, at a site where parental permission is required, die or no longer be reasonably available for any reason, no further study-specific visits or procedures may be performed until informed consent for continued study participation is obtained from a locally authorized guardian. In accordance with the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research (available at the website referenced in Section 12.2), all study sites must establish and maintain written procedures describing the standards that will be followed to identify who may serve as guardian for an enrolled participant, reflective of applicable IRB/EC guidance for conduct of human subjects research within the context of available local law, regulation, or government policy.

12.4 Potential Benefits

Participants in this study may experience no direct benefit. The study may help participants gain skills to assess and monitor their depression symptoms and improve their levels of functioning through the use of medication and therapy. Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to the development of medication guidelines and H&W CBT tailored for youth living with HIV. Participants also may appreciate the opportunity to contribute to the field of HIV and depression research. Participants will receive laboratory testing and treatment counseling. For other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to other sources of care available in their community. Some participants may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of abnormalities identified during tests, examinations and referrals.

12.5 Potential Risks

12.5.1 General

It is not expected that this trial will expose participants to unreasonable risk. Phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection. Participants may experience discomfort when answering questions of a personal nature, such as questions dealing with sexual behaviors.

Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as HIV-positive). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

12.5.2 Unimproved depression or clinical deterioration

Continued depression or worsening of depressive symptoms is always a risk of depression regardless of use of medication and/or counseling. In addition, as suicidal ideation is a symptom of depression, suicide or suicide attempt is a risk. Clinical deterioration due to the underlying psychiatric condition(s), or the study interventions themselves (CBT therapy, MM algorithm; ESC), is also a risk. These risks will be assessed during MM visits with the site prescribing clinician who will be monitoring the participant's depression symptoms using the QIDS-SR regardless of the use of medication. The H&W CBT therapist will also be monitoring depression symptoms during H&W CBT visits. ESC therapists and clinicians will likewise be monitoring depression symptoms as per their usual standard of care.

12.5.3 Medication side effects

Although this protocol is not providing medications directly to participants; participants may be using antiretroviral and/or anti-depressive medication during the course of the study. Common and rare side effects of antidepressants and any other adjunctive medications that are prescribed will be discussed with the participant by the site prescribing clinician.

Participants will be informed that they are free to decline starting medications or stop taking medications at any time without penalty. Participants who start new medications while on study may have more frequent study visits as determined by the site prescribing clinician. Site prescribing clinicians will request any clinically indicated laboratory tests including hematology, chemistry panel (including: Ca, PO4, Cr, Liver tests (AST, ALT, Albumin, Bilirubin, Alkaline Phosphatase) and electrolytes (Na, K, Cl, HCO3)), lithium levels and an electrocardiogram) per standard of care for the antidepressant prescribed. All grade 3 or higher adverse effects relating to medications will be reported to the protocol team, using the Adverse Event form.

12.5.4 Drug-drug interaction

Drug-drug interactions among antidepressants and ARV treatments will be considered and clinically monitored. While there are no antidepressants specifically contra-indicated with ARV treatments, the pharmacological characteristics of antidepressants are important to consider as such interactions can result in significant consequences (e.g. lowering of ARV blood levels leading to reduced efficacy, increasing serotonin levels with the potential for serotonin syndrome, etc).

12.5.5 Complications with pregnancy

There is a risk that antidepressant medications may cause birth defects including fetal growth changes, shorter gestations, neonatal irritability, neurobehavioral changes and problems with fetal breathing in female participants who become pregnant while participating in the study. Although there is some concern regarding the use of SSRIs during pregnancy and their effects on the growing fetus, research results are not conclusive. There is also a risk that antidepressant medications may cause changes in sperm in males. All participants, who are sexually active, will be recommended to use condoms because of the risk in pregnancy and STI transmission.

Female participants who become pregnant during the study, or who are at high risk of becoming pregnant, may continue in the study, and site investigators will counsel them on continued use of antidepressants in accordance with best clinical judgment and standard care practices.

Furthermore, study staff will refer pregnant participants, or treat them, according to the Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Peri-natal HIV Transmission in the United States: dated June 7, 2016 (https://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0#); and register them in the Antiretroviral Pregnancy Registry as per Section 6.8.

Regardless of action taken with medications, all participants will continue to be followed in the study and remain in their assigned groups for the purposes of analysis.

12.6 Reimbursement/Compensation

Pending IRB/EC approval, participants will be compensated for time and effort in this study, and/or be reimbursed for travel to study visits. Site specific reimbursement amounts will be specified in the study informed consent forms of each individual site.

12.7 Privacy and Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. The information a participant provides during study visits will not be shared routinely with their parent/guardian, unless the participant and site staff agree that this is important for their well-being. Sites should follow their SOPs and standard of care to involve parents/guardians when appropriate. Sites will inform potential participants about any limits to confidentiality, including state laws that require reporting of abuse or harm to the participant or others.

Each study site will implement confidentiality representatives to identify potential confidentiality issues and strategies to address them. In addition to local considerations, the protections described below will be implemented at all sites.

All study-related information will be stored securely. All participant information will be stored in locked areas with access limited to study staff. All laboratory specimens, study data collection, and administrative forms will be identified by coded (PID) number only to maintain participant confidentiality. Study sites are encouraged but not required by DAIDS policies to store study records that bear participant names or other personal identifiers separately from records identified by PID. Forms, lists, logbooks, appointment books, and any other listings that link participants' ID numbers to identifying information will be stored in a separate, locked file in an area with limited access. After receiving appropriate approval, all study documents/data will be properly disposed of, including the proper destruction and/or deletion of paper files, electronic study data, and electronic documents. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following:

- Representatives of the U.S. Federal Government, including OHRP, NIH, and/or contractors of the NIH
- Representatives of the IMPAACT Operations Center, SDMC, and/or Laboratory Center (LC)
- Study staff
- Site IRBs

In addition to the above, a Certificate of Confidentiality has been obtained for this study from the U.S. Department of Health and Human Services. This certificate protects study staff from being compelled to disclose study-related information by any U.S. Federal, state, or local civil, criminal, administrative, legislative, or other proceedings. It thus serves to protect the identity and privacy of study participants.

12.8 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases, including HIV-1, identified among study participants to health authorities. Participants will be made aware of reporting requirements during the informed consent process.

12.9 Management of Incidental Findings

Site staff will inform participants of all exam findings and clinically meaningful laboratory test results. When applicable, site staff will provide referral to non-study sources of medical care for further evaluation and/or treatment of these findings.

12.10 Management of New Information Pertinent to Study Participation

Participants enrolled in the study will receive new information learned during the course of the study that is pertinent and might affect their willingness to remain in the study.

13 ADMINISTRATIVE PROCEDURES

13.1 Regulatory Oversight

This study is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development (NICHD), and National Institute of Mental Health (NIMH), which are part of the United States National Institutes of Health (NIH). The Division of AIDS (DAIDS) within the NIAID is responsible for regulatory oversight of this study. NIAID and NICHD provide funding support to the clinical research sites at which this study will be conducted. Each institute contracts with clinical site monitors who will perform on-site monitoring visits as described in Section 11.0. As part of these visits, monitors will inspect site files to ensure compliance with both US and local regulatory requirements.

13.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) WILL NOT be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

13.3 Study Implementation

This study will be conducted in accordance with the protocol, international good clinical practice guidelines (ICH E6), and all applicable U.S. and local regulations. Study implementation at all sites will also be guided by the study-specific MOP, Laboratory Processing Chart (LPC), and other study implementation materials, which will be available on the IMPAACT web site: www.impaactnetwork.org.

Study implementation at each site will also be guided site-specific standard operating procedures (SOPs). The DAIDS policy on Requirements for Manual of Operational specifies the minimum set of SOPs that must be established at sites conducting DAIDS funded and/or sponsored clinical trials (available on the website referenced in Section 10.2). These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

13.4 Protocol Deviation Reporting

Per the policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available at the website referenced in Section 10.2), all protocol deviations must be documented in participant research records. Reasons for the deviations and corrective and preventive actions taken in response to the deviations should also be documented.

Deviations should be reported to site IRBs/ECs and other applicable regulatory entities in accordance with the policies and procedures of these review bodies. Serious deviations that are associated with increased risk to one or more study participants and/or significant impacts on the integrity of study data must also be reported within IMPAACT, following procedures specified in the IMPAACT Manual of Procedures (which is available on the IMPAACT website: www.impaactnetwork.org).

13.5 Critical Events Reporting

DAIDS has developed a critical event reporting system. Per the policy, critical events include the following:

- Unanticipated Problems
- Serious or Continuing Noncompliance
- Suspension or Termination of IRB/EC Approval
- Suspected Research Misconduct

Additional details on site responsibilities for identification and classification of critical events, the critical events manual, and associated appendices can be found at:

http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/Safety.aspx

All critical event reporting questions should be directed to the site's OCSO representative.

13.6 ClinicalTrials.gov

This protocol is not subject to the Food and Drug Administration Amendments Act of 2007 (FDAAA). However, it will be registered in https://clinicaltrials.gov/ to meet International Committee of Medical Journal Editors (ICMJE) requirements.

14 PUBLICATIONS

DAIDS/NIAID and IMPAACT policies will govern publication of the results of this study.

15 REFERENCES

1. Brown L, Whiteley, L., Harper, G., Nichols, S., Nieves, A. & Adolescent Trials Network for HIV/AIDS Interventions: . Psychological symptoms among 2,032 youth living with HIV: A multisite study. AIDS patient care and STDs. 2014.
2. Burnam MA, Bing EG, Morton SC, Sherbourne C, Fleishman JA, London AS, et al. Use of mental health and substance abuse treatment services among adults with HIV in the United States. Archives of general psychiatry. 2001;58(8):729-36.
3. Vitiello B, Burnam MA, Bing EG, Beckman R, Shapiro MF. Use of psychotropic medications among HIV-infected patients in the United States. The American journal of psychiatry. 2003;160(3):547-54.
4. Bing EG, Burnam MA, Longshore D, Fleishman JA, Sherbourne CD, London AS, et al. Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. Archives of general psychiatry. 2001;58(8):721-8.
5. Cowley D, Gray LR, Wesselingh SL, Gorry PR, Churchill MJ. Genetic and functional heterogeneity of CNS-derived tat alleles from patients with HIV-associated dementia. Journal of neurovirology. 2011;17(1):70-81.
6. Gray LR, Gabuzda D, Cowley D, Ellett A, Chiavaroli L, Wesselingh SL, et al. CD4 and MHC class 1 down-modulation activities of nef alleles from brain- and lymphoid tissue-derived primary HIV-1 isolates. Journal of neurovirology. 2011;17(1):82-91.
7. Boivin MJ, Ruel TD, Boal HE, Bangirana P, Cao H, Eller LA, et al. HIV-subtype A is associated with poorer neuropsychological performance compared with subtype D in antiretroviral therapy-naive Ugandan children. Aids. 2010;24(8):1163-70.
8. de Kloet CS, Vermetten E, Bikker A, Meulman E, Geuze E, Kavelaars A, et al. Leukocyte glucocorticoid receptor expression and immunoregulation in veterans with and without post-traumatic stress disorder. Molecular psychiatry. 2007;12(5):443-53.
9. Kapetanovic S, Aaron L, Montepiedra G, Burchett SK, Kovacs A. T-cell activation and neurodevelopmental outcomes in perinatally HIV-infected children. AIDS. 2012;26(8):959-69.
10. Kapetanovic S, Griner R, Zeldow B, Nichols S, Leister E, Gelbard HA, et al. Biomarkers and neurodevelopment in perinatally HIV-infected or exposed youth: a structural equation model analysis. Aids. 2014;28(3):355-64.
11. Lemieux A, Coe CL, Carnes M. Symptom Severity Predicts Degree of T Cell Activation In Adult Women Following Childhood Maltreatment. Brain, behavior, and immunity. 2008;22(6):994-1003.
12. Uher R, Tansey KE, Dew T, Maier W, Mors O, Hauser J, et al. An Inflammatory Biomarker as a Differential Predictor of Outcome of Depression Treatment With Escitalopram and Nortriptyline. The American journal of psychiatry. 2014.
13. Gadow KD, Chernoff M, Williams PL, Brouwers P, Morse E, Heston J, et al. Co-occuring psychiatric symptoms in children perinatally infected with HIV and peer comparison sample. J Dev Behav Pediatr. 2010;31(2):116-28.
14. Horberg MA, Silverberg MJ, Hurley LB, Towner WJ, Klein DB, Bersoff-Matcha S, et al. Effects of depression and selective serotonin reuptake inhibitor use on adherence to highly active antiretroviral therapy and on clinical outcomes in HIV-infected patients. Journal of acquired immune deficiency syndromes (1999). 2008;47(3):384-90.
15. (APA) APA. Practice Guideline for the Treatment of Patients with HIV/AIDS. 2000.
16. Birmaher B, Brent D, Bernet W, Bukstein O, Walter H, Benson RS, et al. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. Journal of the American Academy of Child and Adolescent Psychiatry. 2007;46(11):1503-26.

17. March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. Jama. 2004;292(7):807-20.
18. Katon WJ, Lin EHB, Von Korff M, Ciechanowski P, Ludman EJ, Young B, et al. Collaborative Care for Patients with Depression and Chronic Illnesses. New England Journal of Medicine. 2010;363(27):2611-20.
19. Menchetti M, Sighinolfi C, Di Michele V, Peloso P, Nespeca C, Bandieri PV, et al. Effectiveness of collaborative care for depression in Italy. A randomized controlled trial. General hospital psychiatry. 2013;35(6):579-86.
20. Cheung AH, Zuckerbrot RA, Jensen PS, Ghalib K, Laraque D, Stein RE. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): II. Treatment and ongoing management. Pediatrics. 2007;120(5):e1313-26.
21. Kadivar H, Garvie PA, Sinnock C, Heston JD, Flynn PM. Psychosocial profile of HIV-infected adolescents in a Southern US urban cohort. AIDS care. 2006;18(6):544-9.
22. Misdrahi D, Vila G, Funk-Brentano I, Tardieu M, Blanche S, Mouren-Simeoni MC. DSM-IV mental disorders and neurological complications in children and adolescents with human immunodeficiency virus type 1 infection (HIV-1). European psychiatry : the journal of the Association of European Psychiatrists. 2004;19(3):182-4.
23. Pao M, Lyon M, D'Angelo LJ, Schuman WB, Tipnis T, Mrazek DA. Psychiatric diagnoses in adolescents seropositive for the human immunodeficiency virus. Archives of pediatrics & adolescent medicine. 2000;154(3):240-4.
24. Ferrando SJ. Psychopharmacologic treatment of patients with HIV/AIDS. Current psychiatry reports. 2009;11(3):235-42.
25. (APA) APA. Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition. 2010.
26. Stone M, Laughren T, Jones ML, Levenson M, Holland PC, Hughes A, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration2009 2009-08-11 23:06:19.
27. Hinton DE, Rivera EI, Hofmann SG, Barlow DH, Otto MW. Adapting CBT for traumatized refugees and ethnic minority patients: examples from culturally adapted CBT (CA-CBT). Transcultural psychiatry. 2012;49(2):340-65.
28. Greer JA, Park ER, Prigerson HG, Safren SA. Tailoring Cognitive-Behavioral Therapy to Treat Anxiety Comorbid with Advanced Cancer. Journal of cognitive psychotherapy. 2010;24(4):294-313.
29. Sauter FM, Heyne D, Michiel Westenberg P. Cognitive Behavior Therapy for Anxious Adolescents: Developmental Influences on Treatment Design and Delivery. Clinical Child and Family Psychology Review. 2009;12(4):310-35.
30. Fischer-Smith T, Tedaldi EM, Rappaport J. CD163/CD16 co-expression by circulating monocytes/macrophages in HIV: potential biomarkers for HIV infection and AIDS progression. AIDS research and human retroviruses. 2008;24(3):417-21.
31. Castley A, Berry C, French M, Fernandez S, Krueger R, Nolan D. Elevated plasma soluble CD14 and skewed CD16+ monocyte distribution persist despite normalisation of soluble CD163 and CXCL10 by effective HIV therapy: a changing paradigm for routine HIV laboratory monitoring? PloS one. 2014;9(12):e115226.
32. Borges AH, Weitz JI, Collins G, Baker JV, Levy Y, Davey RT, Jr., et al. Markers of inflammation and activation of coagulation are associated with anaemia in antiretroviral-treated HIV disease. Aids. 2014;28(12):1791-6.
33. Boulware DR, Hullsiek KH, Puronen CE, Rupert A, Baker JV, French MA, et al. Higher levels of CRP, D-dimer, IL-6, and hyaluronic acid before initiation of antiretroviral therapy (ART) are associated with increased risk of AIDS or death. The Journal of infectious diseases. 2011;203(11):1637-46.

34. Group TISS. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. New England Journal of Medicine. 2015;373(9):795-807.
35. Emery S, Neuhaus JA, Phillips AN, Babiker A, Cohen CJ, Gatell JM, et al. Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study. J InfectDis. 2008;197(8):1133-44.
36. Severe P, Jean Juste MA, Ambroise A, Eliacin L, Marchand C, Apollon S, et al. Early versus Standard Antiretroviral Therapy for HIV-Infected Adults in Haiti. New England Journal of Medicine. 2010;363(3):257-65.
37. Grinsztejn B, Hosseinipour MC, Ribaudo HJ, Swindells S, Eron J, Chen YQ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. The Lancet Infectious diseases. 2014;14(4):281-90.
38. Baker JV, Neuhaus J, Duprez D, Kuller LH, Tracy R, Belloso WH, et al. Changes in inflammatory and coagulation biomarkers: a randomized comparison of immediate versus deferred antiretroviral therapy in patients with HIV infection. J Acquir Immune Defic Syndr. 2011;56(1):36-43.
39. Baker JV, Lundgren JD. Cardiovascular implications from untreated human immunodeficiency virus infection. European heart journal. 2011;32(8):945-51.
40. Baker JV, Engen NW, Huppler Hullsiek K, Stephan C, Jain MK, Munderi P, et al. Assessment of arterial elasticity among HIV-positive participants with high CD4 cell counts: a substudy of the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. HIV Medicine. 2015;16:109-18.
41. Kennard BD, Emslie GJ, Mayes TL, Nightingale-Teresi J, Nakonezny PA, Hughes JL, et al. Cognitive-Behavioral Therapy to Prevent Relapse in Pediatric Responders to Pharmacotherapy for Major Depressive Disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2008;47(12):1395-404.
42. Safren SA, Hendriksen ES, Mayer KH, Mimiaga MJ, Pickard R, Otto MW. Cognitive-behavioral therapy for HIV medication adherence and depression. Cognitive and behavioral practice. 2004;11(4):415-24.
43. Emslie GJ, Mayes T, Porta G, Vitiello B, Clarke G, Wagner KD, et al. Treatment of Resistant Depression in Adolescents (TORDIA): week 24 outcomes. The American journal of psychiatry. 2010;167(7):782-91.
44. Hughes CW, Emslie GJ, Crismon ML, Posner K, Birmaher B, Ryan N, et al. Texas Children's Medication Algorithm Project: update from Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2007;46(6):667-86.
45. Brent D, Greenhill L, Compton S, Emslie G, Wells K, Walkup J, et al. The Treatment of Adolescent Suicide Attempters (TASA) Study: Predictors of Suicidal Events in an Open Treatment Trial. Journal of the American Academy of Child and Adolescent Psychiatry. 2009;48(10):987-96.
46. Yanofski J, Croarkin P. Choosing Antidepressants for HIV and AIDS Patients: Insights on Safety and Side Effects. Psychiatry (Edgmont). 2008;5(5):61-6.
47. Erickson JL, Velasco JM, Hieken TJ. Compliance with melanoma treatment guidelines in a community teaching hospital: time trends and other variables. Annals of surgical oncology. 2008;15(4):1211-7.
48. Golin CE, Earp J, Tien HC, Stewart P, Porter C, Howie L. A 2-arm, randomized, controlled trial of a motivational interviewing-based intervention to improve adherence to antiretroviral therapy (ART) among patients failing or initiating ART. Journal of acquired immune deficiency syndromes (1999). 2006;42(1):42-51.

49. Parsons JT, Golub SA, Rosof E, Holder C. Motivational Interviewing and Cognitive-Behavioral Intervention to Improve HIV Medication Adherence Among Hazardous Drinkers: A Randomized Controlled Trial. Journal of acquired immune deficiency syndromes (1999). 2007;46(4):443-50.
50. Minnis AM, Muchini A, Shiboski S, Mwale M, Morrison C, Chipato T, et al. Audio computer-assisted self-interviewing in reproductive health research: reliability assessment among women in Harare, Zimbabwe. Contraception. 2007;75(1):59-65.
51. Hewett PC, Mensch BS, Erulkar AS. Consistency in the reporting of sexual behaviour by adolescent girls in Kenya: a comparison of interviewing methods. Sexually transmitted infections. 2004;80 Suppl 2:ii43-8.
52. Langhaug LF CY, Pascoe SJS et al. . Comparing 4 questionnaire delivery methods for collection of self-reported sexual behaviour data in Zimbabwean youth. 2007;17th ISSTDR, 10th IUSTI World Congress.(Seattle, Washington, USA. July 29-Aug 1, 2007.).
53. Mensch BS, Hewett PC, Gregory R, Helleringer S. Sexual behavior and STI/HIV status among adolescents in rural Malawi: an evaluation of the effect of interview mode on reporting. Studies in family planning. 2008;39(4):321-34.
54. Bernstein IH, Rush AJ, Trivedi MH, Hughes CW, Macleod L, Witte BP, et al. Psychometric properties of the Quick Inventory of Depressive Symptomatology in adolescents. International journal of methods in psychiatric research. 2010;19(4):185-94.
55. Moore HK, Hughes CW, Mundt JC, Rush AJ, Macleod L, Emslie GJ, et al. A pilot study of an electronic, adolescent version of the quick inventory of depressive symptomatology. The Journal of clinical psychiatry. 2007;68(9):1436-40.
56. Group WAW. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility. Addiction (Abingdon, England). 2002;97(9):1183-94.
57. Humeniuk R, Ali R, Babor TF, Farrell M, Formigoni ML, Jittiwutikarn J, et al. Validation of the Alcohol, Smoking And Substance Involvement Screening Test (ASSIST). Addiction (Abingdon, England). 2008;103(6):1039-47.
58. Naar-King S, Parsons JT, Murphy DA, Chen X, Harris DR, Belzer ME. Improving health outcomes for youth living with the human immunodeficiency virus: a multisite randomized trial of a motivational intervention targeting multiple risk behaviors. Archives of pediatrics & adolescent medicine. 2009;163(12):1092-8.
59. Brown LK, Whiteley L, Harper GW, Nichols S, Nieves A. Psychological symptoms among 2032 youth living with HIV: a multisite study. AIDS patient care and STDs. 2015;29(4):212-9.
60. Wilson IB, Fowler FJ, Jr., Cosenza CA, Michaud J, Bentkover J, Rana A, et al. Cognitive and field testing of a new set of medication adherence self-report items for HIV care. AIDS and behavior. 2014;18(12):2349-58.
61. Hayes RJ, Moulton LH. Cluster Randomised Trials: Taylor & Francis; 2009.
62. Campbell MK TS, Ramsay CR, MacLennan GS, Grimshaw JM. . Sample size calculator for cluster randomised trials. Comput Biol Med. 2004;34:113-25.

Appendix I: Schedule of Evaluations for All Participants

Study Visit	Screening/ Entry Visit	Week 1	Week 6	Week 12	Week 24	Week 36	Week 48/Study Exit/Early Discontinuation	Interim Visit
Visit Window	—	-7/+14 d	±14 d	±14 d	±14 d	±14 d	±14 d	—
Administrative and Regulatory								
Obtain written informed assent and/or consent	X							
Assign PID number	X							
Collect demographic information	X							
Collect/review locator information	X	X	X	X	X	X	X	X
Assess eligibility	X							
Complete Subject Enrollment System	X							
Behavioral and Counseling								
HIV pre-/post-test counseling	*							
Behavioral questionnaire[+]	X		X	X	X	X	X	
QIDS-SR	X	X~	X~	X~	X	X	X	^~
Client Satisfaction Questionnaire					X			
Physician Satisfaction Questionnaire (COMB-R Sites Only)					X			
Clinical								
Obtain/update medical and medications history	X	X	X	X	X	X	X	*
Assess CDC HIV disease category	X				X	X	X	
Obtain CD4 nadir from medical history	X							
QIDS-C	X							
Provide available findings/test results	X	X	X	X	X	X	X	X
Record/update AEs		X	X	X	X	X	X	X
COMB-R Sites ONLY:								
Review treatment options using MM		X	X	X	X			*
MM Checklist		X	X	X	X			*
CBT Session using CBT Manual		X	X	X	X			*
CBT Adherence Checklist		X	X	X	X			*
ESC Sites ONLY:								
Medication management, as indicated by symptoms		X	X	X	X			*
Psychotherapy, as indicated by symptoms		X	X	X	X			*
ESC therapy Checklist		X	X	X	X			*
Laboratory								
CD4+ T-Cell Count (4mL)	X				X		X	
HIV-1 RNA (4mL)	X				X		X	
Plasma for inflammatory/biomarkers (5 mL)	X				X		X	
HIV-1 test (confirmatory tests as needed) (5mL)[#]	*							
Total blood volumes (may vary depending on local laboratory requirements)	13-18mL				13mL		13mL	

X - required, * - if indicated, ~ administered on paper form only at COMB-R sites, ^ only required at COMB-R sites during interim clinical visits when participants meets with site prescriber, [+] includes sexual, adherence and drug and alcohol use, [#]If HIV RNA PCR is used to establish HIV status at screening /entry, it may be also used as the viral load measure for study entry

Note: Week 1 procedures may be combined with the Screening and Enrollment Visit if convenient for the participant and study staff

Appendix II: Sample Informed Assent

INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS (IMPAACT) NETWORK

SAMPLE INFORMED ASSENT

For protocol:

IMPAACT 2002
COMBINED COGNITIVE BEHAVIORAL THERAPY AND A MEDICATION MANAGEMENT ALGORITHM FOR TREATMENT OF DEPRESSION AMONG YOUTH LIVING WITH HIV IN THE UNITED STATES
Version 1.0, dated 19 August 2016

INTRODUCTION

You are being asked to take part in this research study because you have Human Immunodeficiency Virus (HIV) and may have depression. Before you decide if you want to be a part of this study, we want you to know about the study.

This form gives you information about this study. The decision of being in the study is up to you. Please ask if you have any questions at all. You may choose to stop being in the study at any time. If you agree to take part in this study, you will be asked to sign this form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

This study will test if certain types of counseling help improve depression for youth living with HIV. The study may help you gain skills to help you feel better.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

You will be asked to come to the clinic for 6 additional visits. Also, you may be asked to come for additional counseling visits. How many more visits will be decided based on your needs. You, your parents and your doctor will decide how often you need to come. Also, you may be asked to take medication to help improve your mood.

WHAT WILL HAPPEN AT MY VISITS?

The following things may happen during your study visits:

- We will ask about your health and medications.
- At some visits, you will complete a questionnaire. We will ask you questions about your mood, medications, sexual behavior, drug and alcohol use. Some will be done on a computer. When the interview is complete, the computer "locks in" your information. No one in the clinic can see how you answered the questions. At the end of the study we will ask about what you liked and didn't like about this study.
- A staff member will talk with you about giving you medication to treat your depression. Taking medication for depression is your decision. If you choose not to take medication, you can still participate in the study. Your doctor will also keep taking care of you.
- At some visits, we will draw blood samples to test the amount of HIV in your blood. Other tests will be sent to see how you are doing.
- You will meet with a counselor to learn about treating your depression with counseling.

- We will give you the results of any blood tests, when available.
- These visits will take about *[sites to insert]* to complete.

The information you provide during your visits will not be shared with your parent/guardian, unless you want. But, if we learn something that would put you or others in danger we will share this information with the authorities (hospital, police, or social services).

After you sign this assent form, and we check that you are able to join this study, you will be enrolled, and we will schedule your next visit.

It is important for you to come to every study visit. If you cannot come to the visit, please tell the study staff as soon as possible so that the visit can be rescheduled.

WHAT ARE THE RISKS OF THE STUDY?

- Your depression may not get better, or you may have suicidal thoughts.
- Other possible risks include:
    - Having blood drawn may cause discomfort, dizziness or faintness, bruising, swelling and/or infection.
    - You may become embarrassed and/or worried; study staff will help you with any feelings or questions you have.
    - It is possible that others may learn that you are in this study; we will make every effort to protect your privacy.

WILL BEING IN THIS STUDY HELP ME?

This study might help you and others in the future. It may help you because you:

- Learn ways on how to manage your depression.
- Improve your health and energy level with the use of medication and counseling.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or drop out of the study at any time. You can keep going to your therapist and other doctors for medication treatment and counseling. You will be treated the same no matter what you decide. Your decision will not have any impact on your participation in other studies and will not result in any loss of medical benefits.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

You can ask any questions at any time to the people listed below:

- [Name of the investigator or other study staff]
- [Telephone number of above]

For questions about your rights as a research participant, contact:

- [Name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]
- [Telephone number of above]

SIGNATURE PAGE

If you have read this assent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

ASSENT (For children who are capable of understanding the study procedures and their potential discomforts and benefits).

_____
Minor Participant's Name (Print)

_____ _____
Minor Participant's Signature Date

_____	_____	_____
Study Staff Conducting Assent Process Name (print)	Study Staff Signature	Date
_____	_____	_____
Witness Name	Witness Signature	Date

Appendix III: Sample Informed Consent

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS (IMPAACT) NETWORK

SAMPLE SCREENING, ENROLLMENT, and LONG-TERM STORAGE CONSENT
(Parent/Guardian Form)

For protocol:

IMPAACT 2002
COMBINED COGNITIVE BEHAVIORAL THERAPY AND A MEDICATION MANAGEMENT ALGORITHM FOR TREATMENT OF DEPRESSION AMONG YOUTH LIVING WITH HIV IN THE UNITED STATES
Version 1.0, dated 19 August 2016

INTRODUCTION

Your child is being asked to take part in this research study because s/he is Human Immunodeficiency Virus (HIV)-positive, and may have been diagnosed with depression. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (*insert name of Principal Investigator*). Before you decide if you want your child to be a part of this study, we want you to know about the study.

This consent form gives you information about this study. In order for your child to be in the study, both you and your child must agree to join the study. You are free to ask questions about this study at any time. You may choose to have your child stop being in the study at any time. If you agree for your child to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

This study is being done to find out if a certain type of counseling, called Cognitive Behavioral Therapy, and a certain method to review and suggest using medications, called the Medication Management Algorithm, helps improve depression for youth living with HIV. This study may provide important information about the treatment of depression in HIV-positive youth and young adults. In addition, the study may help your child understand their depression symptoms and improve their health through the use of medication and counseling.

WHAT DOES MY CHILD HAVE TO DO IN THIS STUDY?

If your child joins this study, s/he will be in the study for about one year. You will be asked for ways for study staff to contact you and your child. This contact information will be used to remind you to bring your child to the clinic for study visits. All of the contact information you provide will be stored in a secure and locked area at the study clinic. Study staff will not leave phone or text messages unless you give them permission to do so.

There are two different groups in this study. One group will have the Cognitive Behavioral Therapy and Medication Management sessions (this group is called COMB-R). COMB-R is a specific combination of talk therapy and a medication map. The other group will have enhanced standard of care, which may be like the counseling sessions you currently have (this group is called ESC). If your child is in the COMB-R group, you may be asked to switch to a different study therapist, if their current therapist is not working on this study.

Both groups, COMB-R or ESC, will be asked to come for six additional visits (at Weeks 1, 6, 12, 24, 36 and 48). We may be able to complete the Week 1 procedures today if your child and study staff have time.

Screening/Entry Visit

If you and your child are interested in joining this research study, we will first do some tests to see if your child can participate. If needed, some screening tests may be done more than once.

- We will ask your child about their medical and medication history. This may include questions about their health and symptoms, medications, and illness. We will also get information from his/her medical record.
- We will ask your child to complete questionnaires about their depressive symptoms, use of HIV and depression medications, sexual behavior and drug and alcohol use. They will also meet with a staff member to complete a separate questionnaire that measures their depression symptoms.
- A staff member will talk about giving medication to treat your child's depression. Taking medication for depression is you and your child's choice. If you choose not to, this will not affect your child's participation in the study or their ability to get medical treatment at the clinic.
- We will draw about 18 mL (about three and a half teaspoons) of blood:
  - For HIV testing (if documentation needed for the study is not already available)
  - To test the amount of HIV in their blood
  - To test their CD4+ T-cell count. The CD4+T-cell count is a test that measures the amount of damage HIV has done to the immune system.
  - Some of the blood will used to test for inflammation, which is the body's natural response to an infection like HIV.
- This visit will take about *[sites to insert]* two hours to complete.

After you sign this consent form, and we confirm that your child is able to join this study, s/he will be enrolled. Multiple visits may be needed to understand if your child can participate in the study. This visit will need to be completed in 30 days.

Assessment Visits: Weeks 1, 6, 12, 24, 36 and 48

Participants will have six visits at the clinic at Weeks 1, 6, 12, 24, 36 and 48. These visits may take up to two hours. At these visits the following will be done:

- Your child will be asked to update their contact information.
- Your child will be asked to complete a questionnaire about their depressive symptoms.
- Your child will meet with a site therapist and other doctors, to learn about treating their depression with counseling and medication, if needed.
- We will review any laboratory test results, and current medications taken for HIV or depression since the last study visit.
- Your child will be asked to complete a questionnaire about the medications they may be taking (for HIV and/or depression), sexual behavior, and drug and alcohol use.
- At one visit about halfway through the study, your child will be asked to complete a questionnaire about their satisfaction with the therapy, including the procedures, quality and quantity of service, outcome, and general satisfaction
- At some visits, your child will have about 15 mL (about three teaspoons) of blood drawn:
  - To test the amount of HIV in their blood
  - To test their CD4+ T-cell count
  - To test for markers of inflammation.
- We will give your child the results of these tests, when available.

It is important for your child to come to every study visit. If they cannot come to the visit, please tell the study staff as soon as possible so that the visit can be rescheduled.

Interim Visits
In addition to the visits listed above, your child may be encouraged to come to additional visits in between for counseling and treatment. These are called interim visits. You, your child and the doctor will decide how often those visits will happen. They may be as often as every week depending on your child's needs. While these visits are not mandatory, they may help your child improve their depressive symptoms.

Computer-Assisted Self-Interviews
Some of the questionnaires will be done on a computer using a program called Audio Computer-Assisted Self-Interview (ACASI). ACASI uses a computer so your child can see (on the screen) each question and then answer choices for that question. When the interview is complete, the computer "locks in" the information so no one at the clinic can see how you answered.

Your child does not have to answer any question that they don't want to and can end the computer interview at any time if they do not want to continue. No one will be able to look at any of their answers once they have answered all questions in each section. Once they have finished all the questions, the whole interview will be locked and will be kept confidential. No information that identifies your child is collected during the computer session; only their study ID number will be recorded.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
There will be about 156 participants, ages 12 to 24, in this study. There will be about ten study participants at this site.

HOW LONG WILL MY CHILD BE IN THIS STUDY?
Your child will be in this study for about one year.

WHY WOULD THE DOCTOR TAKE MY CHILD OFF THIS STUDY EARLY?
The study doctor may need to take your child off the study early without your permission if:
- The study is cancelled by the National Institutes of Health (NIH), IMPAACT, and local regulatory authorities, the Office for Human Research Protections (OHRP), or the site's Institutional Review Board (IRB) or Ethics Committee (EC). An IRB/EC is a committee that watches over the safety and rights of research participants.
- Your child is not able to attend the study visits as required by the study.
- The study doctor determines that further participation in the study would be harmful to your child's health or well-being.
- If your child is taken off this study early for any reason, your child will be asked to return to clinic for one last visit if they are available.

WHAT ARE THE RISKS OF THE STUDY?
Unimproved depression or worsening of symptoms
Continued depression or worsening of depressive symptoms is always a risk of depression regardless of use of medication. In addition, suicide or suicide attempt is a risk of depression. These risks will be reviewed during clinic visits with the site doctor who will be monitoring your child's depression symptoms. If your child agrees to take medication, they may have additional lab tests done and monitored, as is the usual standard of care.

Medication side effects
Your child is free to decide not to start, or stop, taking antidepressant medications at any time during this study. All medications that may be prescribed while your child is in this study are approved for treatment of depression. In general, medications for depression are safe. If your child chooses to start taking a medication to treat depression, they may experience side effects. They will discuss these potential side effects with their doctor. Common side effects of antidepressants may include nausea, vomiting, feeling tired, feeling dizzy, feeling nervous, loss of appetite, increased appetite, trouble sleeping, dry mouth, headache, changes in interest in sex, feeling thirsty, upset stomach, or runny nose.

Drug-drug interaction
If your child is taking antidepressant medications and also HIV medications, it is possible that they could mix with each other in a negative way. While this is unlikely to happen, your child's doctors will look for any signs that the medications are not working well together.

Complications with pregnancy
There is a risk that antidepressant medications cause birth defects. If your child becomes pregnant during the study, she may continue in the study, and site staff will discuss use of antidepressants based on the doctor's advice. Your child's doctor may also report their pregnancy to the Antiretroviral Pregnancy Registry. The Antiretroviral Pregnancy Registry assists patients and doctors in gauging potential benefits and risks of treatment; however, the registry does not collect any identifying information about your child, such as name, initials, contact information, or date of birth. There is a risk that antidepressant medications may cause changes in sperm in males. All participants, who are sexually active, will be recommended to use condoms because of the risk in pregnancy and of STI transmission.

Other Possible Risks
Having blood drawn may cause discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection.

Your child may become embarrassed and/or worried when talking to therapists and other site staff. They may be worried while waiting for test results. Trained study staff will help your child with any feelings or questions they have.

We will make every effort to protect your child's privacy. Their visits will take place in private. However, it is possible that others may learn that your child is in the study, and because of this, may treat your child unfairly. For example, s/he may feel uncomfortable at school, may have problems getting or keeping a job, or being accepted by their family, friends, or community. If your child has any problems, site staff will talk with them, to try to help resolve them.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
There is no guarantee that your child will benefit from taking part in the study, but participating in the study may help them:

- Learn how to monitor their depression symptoms**;** and
- Improve their overall health through the use of medication and counseling.

Also, the results from this study may provide important information about the treatment of depression in HIV positive youth.

WHAT ABOUT CONFIDENTIALITY?
We will make every effort to keep your child's personal information confidential. We cannot guarantee absolute confidentiality. The information your child provides during their visits will not be shared with

you, unless your child and doctor want us to. If the study staff learns of possible child abuse and/or neglect or a risk of harm to your child or others, they will be required to tell the proper authorities. Any publication of this study will not use your child's name.

Your child's records may be reviewed by the [insert name of site] IRB/EC, National Institutes of Health (NIH), Office for Human Research Protections (OHRP), study staff, and study monitors.

In addition to the efforts of the study staff to help keep personal information private, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your child's participation or information given for study purposes. This certificate does not prevent you from releasing information about yourself or your child and your child's participation in the study.

ARE THERE ALTERNATIVES TO THIS STUDY?

You may choose for your child to not take part in this study. Your child can keep going to their therapist and other doctors for medication treatment and counseling. [*Sites to insert if applicable*]: There may be other studies going on here or in the community that your child may be eligible for. If you wish, we will tell you about those other studies.

WHAT ARE THE COSTS TO ME?

You and your child will not be charged for any study visits. Your child may get recommendations for medications or medical treatments to help with their depression as part of this study. However, the costs for medications, treatments, or laboratory tests will be charged to you or your health insurance company as would normally be done for your medical care. It cannot be promised that the risks you were told about or other unknown problems will not happen. There will be appropriate clinic staff available for you to speak with if you or your child become upset at any time during the study. Any further care or treatment after your child is no longer in the study will be charged to you or your health insurance company as would be done for routine medical care.

REIMBURSEMENT

[*Sites to insert information about local reimbursement*:] Your child will get [*Sites to insert amount $xx*] for their time, effort, and travel to and from the clinic at each scheduled visit. They may receive [*Sites to insert amount $xx*] for any visits which occur in between their normally scheduled visits.

WHAT HAPPENS IF YOUR CHILD IS INJURED?

We do not expect anyone to get injured by participating in this study. If your child is injured or becomes ill from taking part in this study, it is important to tell their study doctor and we will help your child get the medical care they need. Treatment may be needed, and the cost of treatment would be charged to you, or your insurance company, as would normally be done for your medical care. No monetary compensation (payment to you) or other forms of compensation for such injuries will be provided by the *[Name of Institution]* or sponsor (NIH).

WHAT ARE MY CHILD'S RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose for your child to not take part in this study or drop out of the study at any time. You and your child will be treated the same no matter what you decide. Your decision will not have any impact on your child's participation in other studies and will not result in any penalty or loss of benefits.

We will tell you about new information from this or other studies that may affect your child's health, welfare or willingness to stay in this study. If you want the results from this study, let the study staff know. A description of this clinical trial is available on http://www.ClinicalTrials.gov. This website will

not include information that can identify you. Once available, the website will include a summary of the results. You can search this website at any time.

CONSENT FOR STORAGE AND FUTURE TESTING OF SPECIMENS and RELATED HEALTH INFORMATION

There might be a small amount of your child's blood left over after we have done all of the study related testing. We would like to ask your permission to store their leftover blood and related health information for use in future studies. If you and your child agree, their samples and related health data will be stored safely and securely. Only approved researchers will have access to the samples. There is no time limit on how long your samples will be stored. The specific type of testing planned for these specimens is not yet known. Any future testing will also have to be approved by an Ethics Committee/ Institutional Review Board. No genetic testing (limited or genome-wide) is planned.

Your child can still enroll in this study if you decide not to have blood stored for future studies. You can withdraw your consent for the storage and future testing of specimens at any time by providing your request in writing to the person in charge of this study, and the leftover samples will be destroyed. If your child becomes an adult and decides that they want the specimens withdrawn, then they may follow the same procedure of providing a request in writing to the person in charge of the study. However, researchers will not be able to destroy samples or information from research that is already underway.

PARENT/GUARDIAN INITIALS

_____ Initials	I DO agree to allow my child's biological specimens and health data to be stored and used in future research studies.
_____ Date	
_____ Initials	I DO NOT agree to allow my child's biological specimens and health data to be stored and used in future research studies.
_____ Date	

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- [Name of the investigator or other study staff]
- [Telephone number of above]

For questions about your child's rights as a research participant, contact:

- [Name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]
- [Telephone number of above]

SIGNATURE PAGE

I have read this consent form (or had it explained to me), and all my questions have been answered.

I voluntarily agree to allow my child, to whom I am the legal guardian, to be in this research study.

Parent's or Guardian's Name (Print)	Relationship to Participant (Child)
Parent's or Guardian's Signature	Date

Study Staff Conducting Consent Process Name (print)	Study Staff Signature	Date
Witness Name	Witness Signature	Date

Appendix IV: Sample Participant Informed Consent

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS (IMPAACT) NETWORK

SAMPLE SCREENING, ENROLLMENT, and LONG-TERM STORAGE CONSENT
(for emancipated minors, participants above legal age of consent, or for participants at study sites that have obtained a waiver of parental permission)

For protocol:

IMPAACT 2002
COMBINED COGNITIVE BEHAVIORAL THERAPY AND A MEDICATION MANAGEMENT ALGORITHM FOR TREATMENT OF DEPRESSION AMONG YOUTH LIVING WITH HIV IN THE UNITED STATES
Version 1.0, dated 19 August 2016

INTRODUCTION

You are being asked to take part in this research study because you have been told that you are Human Immunodeficiency Virus (HIV)-positive, and may have been diagnosed with depression. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (*insert name of Principal Investigator*). Before you decide if you want to be a part of this study, we want you to know about the study.

This consent form gives you information about this study. The study staff will talk with you about this information. In order for you to be in the study, you must agree to join the study. You are free to ask questions about this study at any time. You may choose to stop being in the study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

This study is being done to find out if a certain type of counseling, called Cognitive Behavioral Therapy, and a certain method to review and suggest using medications, called the Medication Management Algorithm, helps improve depression for youth living with HIV. This study may provide important information about the treatment of depression in HIV-positive youth and young adults. In addition, the study may help you understand your depression symptoms and improve your overall health through the use of medication and counseling.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

If you join this study, you will be in the study for about one year. You will be asked for ways for study staff to contact you so that you can be reminded to come to the clinic for your study visits. You will not be forced to give any contact information that you don't want to give. All of the contact information you provide will be stored in a secure, locked, area at the study clinic. Study staff will not leave phone or text messages unless you give them permission to do so.

There are two different groups in this study. One group will have the Cognitive Behavioral Therapy and Medication Management sessions (this group is called COMB-R). The other group will have enhanced standard of care, which may be like the counseling sessions you currently have (this group is called ESC). If you are in the COMB-R group, you may be asked to switch to a different study therapist, if your current therapist is not working on this study.

Both groups, COMB-R or ESC will be asked to come for six additional visits (at Weeks 1, 6, 12, 24, 36 and 48). We may be able to complete the Week 1 procedures today if you and study staff have time.

Screening/Entry Visit

If you are interested in joining this research study, we will first do some tests to see if you can participate. If needed, some screening tests may be done more than once.

- We will ask about your medical and medication history. This may include questions about your health and what symptoms, medications, and illnesses you have had. We will also get information from your medical records.
- We will ask you to complete questionnaires about your depressive symptoms, use of HIV and depression medications, sexual behavior and drug and alcohol use. You will also meet with a staff member to complete a separate questionnaire that measures your depression symptoms.
- A staff member will talk with you about giving medication to treat your depression. Taking medication for depression is your choice. If you choose not to, this will not affect your participation in the study or your ability to get medical treatment at the clinic.
- We will draw about 18 mL (about three and a half teaspoons) of blood:
  - For HIV testing (if documentation needed for the study is not already available)
  - To test the amount of HIV in your blood (your viral load)
  - To test your CD4+ T-cell count. The CD4+T-cell count is a test that measures the amount of damage HIV has done to your immune system. The immune system is the part of the body that fights off germs and infections.
  - Some of the blood will used to test for inflammation, which is the body's natural response to an infection like HIV.
- We will give you the results of your tests, when available. You will get the results of some laboratory tests (e.g., HIV-related tests), but you will not receive results of the research laboratory tests done for this study.
- This visit will take about *[sites to insert]* two hours to complete.

After you sign this consent form, and we confirm that you are able to join this study, you will be enrolled. Multiple visits may be needed to understand if you can participate in the study. This visit needs to be completed in 30 days.

Assessment Visits: Weeks 1, 6, 12, and 24

Participants will have six visits at the clinic at Weeks 1, 6, 12, 24, 36 and 48. These visits may take up to 2 hours [*sites to insert*]. At these visits the following will be done:

- You will be asked to update any information on where you live and how we can contact you.
- You will be asked to complete a questionnaire about your depressive symptoms. Your doctor will review your depressive symptoms and may discuss treating your depression with medication (antidepressants) as needed.
- You will also meet with a site therapist to learn about treating your depression with counseling and medication, if needed.
- We will talk with you and review your medical records to find out about any laboratory test results, and current medications taken for HIV or depression since your last study visit.
- At some visits, you will be asked to complete a questionnaire about the medications you may be taking (for your HIV and/or antidepressants), your sexual behavior, and drug and alcohol use.
- At one visit about halfway through the study, you will be asked to complete a questionnaire about your satisfaction with the therapy, including the procedures, quality and quantity of service, outcome, and general satisfaction

- At some visits, you will have about 15 mL (about three teaspoons) of blood drawn:
  - To test the amount of HIV in your blood
  - To test your CD4+ T-cell count
  - Some of the blood will used for research purposes, to test markers of inflammation in your blood
- We will give you the results of your tests, when available.

It is important for you to come to every study visit. If you cannot come to the visit, please tell the study staff as soon as possible so that the visit can be rescheduled.

Interim Visits
In addition to the visits listed above, you may be encouraged to come to additional visits in between for counseling and treatment. These are called interim visits. You and the doctor will decide how often those visits will happen. They may be as often as every week depending on your needs. While these visits are not mandatory, they may help improve your depressive symptoms.

Computer-Assisted Self-Interviews
Some of the questionnaires you complete during this study will be done on a computer using a program called Audio Computer-Assisted Self-Interview (ACASI). ACASI uses a computer so you can see (on the screen) each question and the answer choices for that question. You will enter your answer right into the computer. When the interview is complete, the computer "locks in" your information so no one at the clinic can see how you answered.

You do not have to answer any question that you don't want to and you can end the computer interview at any time if you do not want to continue. No one will be able to look at any of your answers once you have answered all questions in each section. Once you have finished all the questions, the whole interview will be locked and will be kept confidential. No information that identifies you is collected during the computer session; only your study ID number will be recorded.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
There will be about 156 participants, ages 12 to 24, in this study. There will be about 10 study participants at this site.

HOW LONG WILL I BE IN THIS STUDY?
You will be in this study for about one year.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?
The study doctor may need to take you off the study early without your permission if:
- The study is cancelled by the National Institutes of Health (NIH), IMPAACT, and local regulatory authorities, the Office for Human Research Protections (OHRP), or the site's Institutional Review Board (IRB) or Ethics Committee (EC). An IRB/EC is a committee that watches over the safety and rights of research participants.
- You are not able to attend the study visits as required by the study.
- The study doctor determines that further participation in the study would be harmful to your health or well-being.
- If you are taken off this study early for any reason, you will be asked to return to clinic for one final visit, if you are available

WHAT ARE THE RISKS OF THE STUDY?

Unimproved depression or worsening of symptoms

Continued depression or worsening of depressive symptoms is always a risk of depression regardless of use of medication. In addition, suicide or suicide attempt is a risk of depression. Your symptoms may also get worse due to a psychiatric condition(s). These risks will be reviewed during clinic visits with the site doctor who will be monitoring your depression symptoms. If you agree to take medication, you may have additional lab tests done and monitored, as is the usual standard of care.

Medication side effects

You are free to decide not to start, or stop, taking antidepressant medications at any time during this study. If you start new medications while on study, you may have more study visits if your study doctor thinks it is needed. Your doctors may request that you have laboratory tests depending on the antidepressant(s) that were prescribed for you. If you are taking antidepressant medications, your doctor will discuss the potential side-effects of your specific medications with you.

Drug-drug interaction

If you are taking antidepressant medications and also HIV medications, it is possible that they could mix with each other in a negative way. While this is unlikely to happen, your doctors will look for any signs that your medications are not working well together.

Complications with pregnancy

There is a risk that antidepressant medications may cause birth defects. If you become pregnant during the study, you may continue in the study, and site staff will discuss use of antidepressants based on your doctor's advice. Your doctor may also report your pregnancy to the Antiretroviral Pregnancy Registry. The Antiretroviral Pregnancy Registry assists patients and doctors in gauging potential benefits and risks of treatment; however, the registry does not collect any identifying information about you, such as name, initials, contact information, or date of birth. There is a risk that antidepressant medications may cause changes in sperm in males. All participants, who are sexually active, will be recommended to use condoms because of the risk in pregnancy and of STI transmission.

Other Possible Risks

Having blood drawn may cause you to have discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection.

You may become embarrassed and/or worried when talking to therapists and other site staff. You may be worried while waiting for your test results. Trained study counselors will help you with any feelings or questions you have.

We will make every effort to protect your privacy. Your visits will take place in private. However, it is possible that others may learn that you are in the study, and because of this, may treat you unfairly or discriminate against you. For example, you may feel uncomfortable at school, you could have problems getting or keeping a job, or being accepted by your family, friends, or community. If you have any problems, site staff will talk with you, and your parent if you prefer, to try to help resolve them.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

There is no guarantee that you will benefit from taking part in the study, but participating in the study may help you:

- Learn how to monitor your depression symptoms**;** and
- Improve your overall health through the use of medication and counseling.

Also, the results from this study may provide important information about the treatment of depression in HIV positive youth.

WHAT ABOUT CONFIDENTIALITY?
We will make every effort to keep your personal information confidential. We cannot guarantee absolute confidentiality. The information you provide during study visits will not be shared with anyone, unless you want us to. If the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the [insert name of site] IRB/EC, National Institutes of Health (NIH), Office for Human Research Protections (OHRP), study staff, and study monitors.

In addition to the efforts of the study staff to help keep your personal information private, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give for study purposes. This certificate does not prevent you from releasing information about yourself and your participation in the study.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?
You may choose not to take part in this study. You can keep going to your therapist and other doctors for medication treatment and counseling. [*Sites to insert if applicable*]: There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about those other studies.

WHAT ARE THE COSTS TO ME?
You will not be charged for any study visits. You may get recommendations for medications or medical treatments to help with your depression as part of this study. However, the costs for medications, treatments, or laboratory tests will be charged to you or your health insurance company as would normally be done for your medical care. It cannot be promised that the risks you were told about or other unknown problems will not happen. There will be appropriate clinic staff available for you to speak with if you become upset at any time during the study. Any further care or treatment after you are no longer in the study will be charged to you or your health insurance company as would be done for your routine medical care.

REIMBURSEMENT
[*Sites to insert information about local reimbursement*:] You will get [*Sites to insert amount $xx*] for your time, effort, and travel to and from the clinic at each scheduled visit. You may receive [*Sites to insert amount $xx]* for any visits which occur in between your normally scheduled visits.

WHAT HAPPENS IF I AM INJURED?
We do not expect anyone to get injured by participating in this study. If you become upset by the questions you are asked, you may be referred to a counselor to speak with. If you are injured or become ill from taking part in this study, it is important to tell your study doctor and we will help you get the medical care you need. Treatment may be needed, but the cost of treatment would be charged to you, or your insurance company, as would normally be done for your medical care. No monetary compensation (payment to you) or other forms of compensation for such injuries will be provided by the *[Name of Institution]* or sponsor (NIH).

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or drop out of the study at any time. You will be treated the same no matter what you decide. Your decision will not have any impact on your participation in other studies and will not result in any penalty or loss of benefits.

We will tell you about new information from this or other studies that may affect your health, welfare or your willingness to stay in this study. If you want the results from this study, let the study staff know. A description of this clinical trial is available on http://www.ClinicalTrials.gov. This website will not include information that can identify you. Once available, the website will include a summary of the results. You can search this website at any time.

CONSENT FOR STORAGE AND FUTURE TESTING OF SPECIMENS and RELATED HEALTH INFORMATION

There might be a small amount of blood left over after we have done all of the study related testing for your study visits. We would like to ask your permission to store your leftover blood and related health information for use in future studies. If you agree, your samples and related health data will be stored safely and securely. Only approved researchers will have access to the samples. There is no time limit on how long your samples will be stored. The specific type of testing planned for these specimens is not yet known. Any future testing will also have to be approved by an Ethics Committee/ Institutional Review Board. No genetic testing (limited or genome-wide) is planned.

You can still enroll in this study if you decide not to have blood stored for future studies. You can withdraw your consent for the storage and future testing of specimens at any time by providing your request in writing to the person in charge of this study, and the leftover samples will be destroyed. However, researchers will not be able to destroy samples or information from research that is already underway.

PARTICIPANT INITIALS	
_____ Initials	I DO agree to allow my biological specimens and health data to be stored and used in future research studies.
_____ Date	
_____ Initials	I DO NOT agree to allow my biological specimens and health data to be stored and used in future research studies.
_____ Date	

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- *[Name of the investigator or other study staff]*
- *[Telephone number of above]*

For questions about your rights as a research participant, contact:

- *[Name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]*
- *[Telephone number of above]*

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

Participant's Name (Print)	Participant's Signature	Date
Study Staff Conducting Consent Process Name (print)	Study Staff Signature	Date
Witness Name	Witness Signature	Date