



## **MANUAL OF PROCEDURES (MOP)**

Solid Organ Transplantation in HIV:  
Multi-Site Study  
Version 10.0  
July, 2009

Sponsoring Institution

University of California, San Francisco

Supporting Institution

The National Institute of Allergy  
and Infectious Diseases

Protocol Co-Chairs

Peter Stock, MD (University of California, San Francisco)  
Michelle Roland, MD (University of California, San Francisco)

Statistician

Don Stablein (EMMES Corporation)  
Burc Barin (EMMES Corporation)

Data Manager

Roe Wright (EMMES Corporation)

Project Managers

Rodney Rogers (University of California, San Francisco)  
Helena Diop (National Institute of Allergy and Infectious Diseases)

# 1 TABLE OF CONTENTS

---

<b>1</b>	<b>TABLE OF CONTENTS .....</b>	<b>2</b>
<b>2</b>	<b>PROJECT ORGANIZATION .....</b>	<b>4</b>
2.1	COMMITTEES .....	4
2.2	SITE PARTICIPATION .....	4
2.3	CONTRACT RESEARCH ORGANIZATIONS .....	5
2.4	SERACARE .....	6
2.5	PROTOCOL ACTIVITIES .....	6
<b>3</b>	<b>CONTACT INFORMATION .....</b>	<b>7</b>
3.1	WHO TO CONTACT .....	7
3.2	STUDY ROSTER (PRINCIPAL INVESTIGATORS) .....	8
3.3	STUDY WEBSITE .....	10
<b>4</b>	<b>PARTICIPATING TRANSPLANT CENTERS.....</b>	<b>11</b>
4.1	CLINICAL CLUSTERS.....	11
4.2	ADULT TRANSPLANT CENTERS .....	11
4.3	PEDIATRIC TRANSPLANT CENTERS .....	11
<b>5</b>	<b>RESEARCH SUB-STUDIES.....</b>	<b>12</b>
5.1	OVERVIEW .....	12
<b>6</b>	<b>SITE STUDY TEAMS .....</b>	<b>13</b>
6.1	MEMBERS.....	13
6.2	ROLE OF THE PRINCIPAL INVESTIGATOR.....	14
6.3	ROLE OF THE STUDY COORDINATOR.....	14
<b>7</b>	<b>SUBJECT SELECTION AND ENROLLMENT .....</b>	<b>15</b>
7.1	ELIGIBILITY SCREENING.....	15
7.2	SCREENING AND ENROLLMENT LOG.....	15
7.3	ENROLLMENT PROCEDURES .....	15
7.4	COMBINED LIVER/KIDNEY TRANSPLANTS .....	16
7.5	RETRANSPLANT .....	16
<b>8</b>	<b>DATA COLLECTION.....</b>	<b>17</b>
<b>9</b>	<b>CLINICAL MANAGEMENT PROTOCOLS .....</b>	<b>18</b>
9.1	USE OF INVESTIGATIONAL DRUGS.....	18
9.2	SPECIAL CONSIDERATIONS FOR CHILDREN .....	18
9.3	IMMUNOSUPPRESSION: RECOMMENDED REGIMENS.....	18
9.4	OPPORTUNISTIC INFECTION PROPHYLAXIS: RECOMMENDED REGIMENS.....	18
9.5	OPPORTUNISTIC INFECTION MONITORING GUIDELINES .....	21
9.6	TB PROPHYLAXIS: RECOMMENDED REGIMENS.....	22
9.7	SPECIAL CONSIDERATIONS WITH ANTIRETROVIRALS.....	22
9.8	ANTIRETROVIRAL DOSE ADJUSTMENTS FOR HEPATIC AND RENAL INSUFFICIENCY.....	25
9.9	HBV AND HBIG THERAPY .....	29
9.10	BIOPSY GUIDELINES FOR BLEEDING DISORDERS.....	29
9.11	DIGITAL RECTAL EXAM .....	30
9.12	GUIDELINES FOR REPEATING SEROLOGIES .....	30

<b>10</b>	<b>STUDY VISIT SCHEDULE AND SPECIMENS .....</b>	<b>32</b>
10.1	TIMING OF EVALUATIONS.....	32
10.2	VISIT NUMBERS.....	32
10.3	VISIT WINDOW .....	33
10.4	STUDY VISITS FOR PATIENTS WITH GRAFT FAILURE .....	33
10.5	TRANSPLANTATION AND FOLLOW-UP AT DIFFERENT CENTERS .....	33
10.6	SPECIMENS .....	34
<b>11</b>	<b>APPENDIX A: AACTG DEFINITION OF PANCREATITIS .....</b>	<b>35</b>
<b>12</b>	<b>SAMPLE STANDING ORDER FOR HBIG.....</b>	<b>39</b>

## **2 PROJECT ORGANIZATION**

---

The “Solid Organ Transplantation in HIV: Multi-Site Study” is being funded through a cooperative agreement between the University of California, San Francisco and the National Institute of Allergy and Infectious Diseases (Division of AIDS and Division of Allergy, Immunology, and Transplantation).

### **2.1 COMMITTEES**

#### **2.1.1 Steering Committee**

A Steering Committee has been established that at a minimum, will consist of the Principal Investigator and Co-Investigator from the grantee institution, one of whom will have expertise in transplantation medicine and the other will have expertise in HIV medicine; the Senior Biostatistician from the consortium; one Senior Investigator from the consortium, but not from the grantee institution, rotating on an annual basis; two independent investigators not affiliated with the clinical trial protocol or adjunct studies; two non-scientific members of the public who are not affiliated with the clinical trials either through direct participation or the participation of close contacts (spouses, immediate and extended family, and domestic partners); the NIAID Program Officer or designate; and one additional NIAID staff member from the Division of Allergy, Immunology, and Transplantation. This group will serve as a governing body for the study and approve all scientific decisions. They may seek outside expertise as necessary. Meetings will occur on a bi-annual basis at which time study progress will be reviewed.

#### **2.1.2 Operations Committee**

An Operations Committee will monitor the progress of the trial quarterly. This group consists of the Principal Investigators, NIAID Medical Officers, EMMES Statistician, UCSF Project Manager, NIAID Project Manager, and UCSF clinical coordinator. This group will review data summaries provided by EMMES, focusing on adverse and serious adverse event data and clinical issues.

#### **2.1.3 Data Safety and Monitoring Board (DSMB)**

An independent DSMB, appointed by the NIAID, will review the protocol for study design and issues of Human Subjects protection prior to study implementation. The DSMB will conduct interim administrative, statistical, and safety reviews at least annually thereafter. Additional interim evaluations of accrual, safety, and/or endpoint data will be scheduled as necessary. Serious adverse events will be reviewed to determine if it is safe to continue the study and to report and advise NIAID on trial-related matters.

### **2.2 SITE PARTICIPATION**

The study is comprised of 21 transplant centers across the United States. Each site has an identified Principal Investigator, possibly a co-Principal Investigator(s), as well as selected sub-investigators. Each site will be responsible for recruiting and enrolling patients, delivering protocol-prescribed therapy, collecting and shipping study related specimens to the studies central repository (SeraCare) and collecting follow-up information on patient outcomes. The success of the endeavor depends on the

cooperation of the sites to perform their tasks and responsibilities in an efficient, effective, and timely manner.

## 2.3 CONTRACT RESEARCH ORGANIZATIONS

### 2.3.1 Data and Statistical Center (EMMES)

EMMES will provide centralized data management, statistical support and coordination assistance. Under the direction of UCSF and NIAID, EMMES will provide technical support and data management services to the participating institutions with respect to quality control, uniformity of data collection, management of the collective database, and data analysis. Case Report forms will be entered into the EMMES Internet Data Entry System (IDES). Data reports will be provided to the various committees for periodic review.

### 2.3.2 Site Monitoring (PPD Development)

This research protocol is federally funded; therefore it falls under the auspices of US OHRP Regulations under 45 CFR 46 and must comply with ICH-GCP (Good Clinical Practice). On-site monitoring will be performed by PPD to ensure compliance with protocol specifications, quality control, and accuracy of data recording. Once sites have submitted all the necessary regulatory documents and obtained IRB approval, a site initiation visit will occur. The site initiation visit will consist of the following:

- Review of regulatory documents
- Tour of the facility
- Screening and enrollment procedures
- Data collection
- Specimen collection
- Adverse and Serious Adverse Event reporting

Routine visits will occur on a bi-annual basis to verify the following:

- 1) To verify study subjects are being appropriately consented.
  - **Each** informed consent will be monitored to verify that subjects are consented prior to study related procedures being performed
  - Verify that the informed consent documents used are IRB approved
- 2) To verify that all subjects met protocol inclusion and exclusion criteria
  - A review of each subject's source documentation to verify that subjects enrolled met eligibility criteria of the study protocol
  - **Each** criterion **must** be addressed in the supporting source documents and be available for review by the monitors
- 3) To verify that reportable adverse events (AE) and serious adverse events (SAE) are being captured and reported appropriately
  - The source documentation will be reviewed to verify that SAE/AE(s) are being adequately identified and reported according to the study protocol
  - Safety lab results will be reviewed to verify that they are being appropriately reviewed, assessed and reported
- 4) To verify that the clinical management adheres to the study protocol.
  - Verify that **study protocol specific procedures** are being performed according to the study protocol, as evidenced by the source documentation

- For the **first** subject transplanted at **each site**, 100% of the source documentation will be reviewed to verify that subject's clinical management adheres to the study protocol
- **Targeted Data Points** will be utilized for monitoring subsequent subjects
- Verify documentation of the primary clinical endpoint of subject and graft survival at one-year post transplant, for **each** subject.

## 2.4 SERACARE

SeraCare Research Laboratories will serve as the specimen repository for this study. All research specimens will be shipped to SeraCare for processing and disbursement to study related research laboratories. Further specimen and contact information may be found in the Laboratory Manual.

## 2.5 PROTOCOL ACTIVITIES

UCSF and NIAID will work together to develop mechanisms and procedures to monitor study performance. Both a project manager at UCSF, Rodney Rogers, and a project manager at NIAID, Allison Priore, will manage the trial and be available to answer questions. Regular conference calls will be scheduled for both the Investigators and Coordinators to discuss concerns and ask questions.

## 3 CONTACT INFORMATION

---

### 3.1 WHO TO CONTACT

**For protocol-related questions, questions and information concerning regulatory documentation, center approval, and the participation of prisoners:**

Contact Rodney Rogers (UCSF Project Manager)

- 415-514-2194
- [Rodney.Rogers@ucsfmedctr.org](mailto:Rodney.Rogers@ucsfmedctr.org)

Contact Helena Diop (NIH Project Manager)

- 301-402-7257
- [dioph@niaid.nih.gov](mailto:dioph@niaid.nih.gov)

**For Specimen and laboratory-related questions:**

Contact Rodney Rogers (UCSF Project Manager)

- 415-514-2194
- [Rodney.Rogers@ucsfmedctr.org](mailto:Rodney.Rogers@ucsfmedctr.org)

Contact Bunmi Adewunmi (SeraCare Bioservices)

- 240-306-4111
- [badewunmi@seracare.com](mailto:badewunmi@seracare.com)

**For clinical medical management questions including entry criteria, adverse event management, or medications:**

Contact Dr. Peter Stock at UCSF for transplant related questions

- (415) 353-1551
- [StockP@surgery.ucsf.edu](mailto:StockP@surgery.ucsf.edu)

Contact Dr. Michelle Roland at UCSF for entry criteria, HIV or medication management related questions

- (916) 449-5905
- [Michelle.Roland@cdph.ca.gov](mailto:Michelle.Roland@cdph.ca.gov)

**For serious adverse event reporting:**

Once a Serious Adverse Event Form has been completed in the EMMES database, an email will automatically be generated to notify the appropriate study staff.

Please fax supporting documentation to the EMMES Data Manager. For questions, please contact one of the following personnel:

Roe Wright (EMMES Data Manager)

- Phone: (301) 251-1161 (ext. 2965)
- Fax: (301) 251-1355
- rwright@emmes.com

Helena Diop (NIAID Project Manager)

- (301) 402-7257
- dioph@niaid.nih.gov

**For non-clinical questions about inclusion/exclusion criteria, data management, and registration-related questions:**

Contact Roe Wright at the EMMES Corporation

- (301) 251-1161 (ext. 2965)
- rwright@emmes.com

### **3.2 STUDY ROSTER (PRINCIPAL INVESTIGATORS)**

#### University of California, SF

Peter Stock (PI)

stockp@surgery.ucsf.edu

Michelle Roland (Co-PI)

mroland@php.ucsf.edu

#### Cedars-Sinai, LA

Fred Poordad (PI)

Poordadf@cshs.org

Nicholas Nissen (Co-PI)

nissenn@cshs.org

#### University of Maryland

Robert Redfield (PI)

Redfield@umbi.umd.edu

Stephen Bartlett (Co-PI)

Sbartlett@smail.umaryland.edu

#### Drexel

Anil Kumar (PI – Kidney)

AK59@drexel.edu

Burckhardt Ringe (PI – Liver)

Burckhardt.Ringe@DrexelMed.edu

#### University of Virginia

Timothy Pruett (PI)

Tp2W@virginia.edu

#### University of Pennsylvania

Kim Olthoff (PI)

kim.olthoff@uphs.upenn.edu

Emily Blumberg (Co-PI)

blumbere@mail.med.upenn.edu

#### University of Pittsburgh

Margaret Ragni (PI)

Ragni@msx.dept-med.pitt.edu

Ron Shaprio (Co-PI)

shapiror@msx.upmc.edu

#### Washington Hospital Center

Jimmy Light (PI)

jimmy.a.light@medstar.net

#### Mt. Sinai

Barbara Murphy (PI) Thomas Schiano (Co-PI)	barbara.murphy@mssm.edu
<u>Columbia University</u> Lorna Dove	lmd62@columbia.edu
<u>Georgetown University</u> Lynt Johnson (PI)	hnsol3@gunet.georgetown.edu
<u>University of Chicago</u> Robert Harland (PI)	rharland@surgery.bsd.uchicago.edu
<u>University of Cincinnati</u> Kenneth Sherman (PI)	shermake@ucmail.uc.edu
<u>University of Miami</u> Jorge Diego (PI - Kidney) Andreas Tzakis (PI – Liver) David Roth (Co-PI – Kidney)	JDiego@med.miami.edu atzakis@miami.edu droth@med.miami.edu
<u>Beth Israel Deaconess</u> Douglas Hanto (PI) Michael Wong (Co-PI)	dhanto@bidmc.harvard.edu mwong@bidmc.harvard.edu
<u>Emory University</u> Tom Pearson (PI)	tpearson@emoryhealthcare.org
<u>Rush University</u> David Simon (PI)	David_M_Simon@rush.edu
<u>Tulane University</u> Sander Florman (PI) Douglas Slakey (Co-PI)	Sander.Florman@HCAhealthcare.com Douglas.Slakey@HCAhealthcare.com
<u>Cleveland Clinic</u> John Fung (PI)	fungj@ccf.org
<u>Johns Hopkins</u> Aruna Subramanian (PI)	asubra@jhmi.edu
<u>Northwestern</u> Tina Stosor (PI) Richard Green (Co-PI)	v-stosor@northwestern.edu r-green2@northwestern.edu
<u>Massachusetts General</u> <i>(research lab. Not a study transplant center)</i> Christian Brander (PI)	brander@helix.mgh.harvard.edu

### **3.3 STUDY WEBSITE**

All study related material and information can always be found on the study website located at [www.HIVTransplant.com](http://www.HIVTransplant.com) or [www.emmes.com](http://www.emmes.com). The study website will also contain the most current roster and contact information.

## 4 PARTICIPATING TRANSPLANT CENTERS

### 4.1 CLINICAL CLUSTERS

Clinical Cluster #1	Clinical Cluster #2	Clinical Cluster #3
UCSF	Univ Pittsburgh	Mt. Sinai
Cedars-Sinai	Washington	Georgetown
Univ Maryland	Drexel	Univ. Chicago
Tulane	Univ Pennsylvania	Univ. Cincinnati
Cleveland Clinic	Univ. Virginia	Columbia
Johns Hopkins	Rush	Univ. Miami
	Northwestern	Beth Israel
		Emory

### 4.2 ADULT TRANSPLANT CENTERS

1. University of California San Francisco (San Francisco, CA)	Kidney, Liver
2. Cedars-Sinai (Los Angeles, CA)	Liver
3. University of Maryland (Baltimore, MD)	Kidney
4. University of Pittsburgh (Pittsburgh, PA)	Liver
5. Washington Hospital Center (Washington, DC)	Kidney
6. Drexel (Philadelphia, PA)	Liver
7. University of Pennsylvania (Philadelphia, PA)	Kidney, Liver
8. University of Virginia (Charlottesville, VA)	Kidney, Liver
9. Mt. Sinai Medical Center (New York, NY)	Kidney, Liver
10. Georgetown University (Washington, DC)	Kidney, Liver
11. University of Cincinnati (Cincinnati, OH)	Kidney, Liver
12. Columbia University (New York, NY)	Liver
13. University of Miami (Miami, FL)	Kidney, Liver
14. University of Chicago (Chicago, IL)	Kidney, Liver
15. Beth Israel Deaconess (Boston, MA)	Kidney, Liver
16. Emory University (Atlanta, GA)	Kidney
17. Tulane University (New Orleans, LA)	Kidney, Liver
18. Rush University (Chicago, IL)	Kidney, Liver
19. Cleveland Clinic (Cleveland, OH)	Kidney, Liver
20. Johns Hopkins (Baltimore, MD)	Kidney, Liver
21. Northwestern (Chicago, IL)	Kidney, Liver

### 4.3 PEDIATRIC TRANSPLANT CENTERS

1. University of California San Francisco (San Francisco, CA)	Kidney, Liver
2. Mt. Sinai Medical Center (New York, NY)	Kidney
3. Columbia University (New York, NY)	Liver
4. University of Chicago (Chicago, IL)	Kidney
5. Tulane (New Orleans, LA)	Kidney, Liver
6. Georgetown University (Washington, DC)	Kidney, Liver

## **5 RESEARCH SUB-STUDIES**

---

### **5.1 OVERVIEW**

Transplant centers will participate in the protocol sub-studies based on which clinical cluster the transplant center is assigned (see section 4.1).

#### **5.1.1 Hepatitis C (HCV)**

All HCV+ patients in all clinical clusters

#### **5.1.2 Hepatitis B (HBV)**

All HBV+ patients in all clinical clusters.

#### **5.1.3 Co-Pathogen Immunology (Cytokine Flow Cytometry and ELISPOT)**

All centers in all clinical clusters

#### **5.1.4 Herpes Virus Virology**

All centers in all clinical clusters

#### **5.1.5 Transplant Immunology (Alloimmune Response)**

All centers in clinical cluster 1

#### **5.1.6 Pharmacokinetics**

UCSF only.

#### **5.1.7 HPV**

UCSF, Cedars-Sinai, University of Maryland, Mt. Sinai liver subjects, Columbia, Beth Israel Deaconess.

#### **5.1.8 HIVAN**

Mt. Sinai, UCSF kidney subjects

## 6 SITE STUDY TEAMS

---

Due to the nature of this study and the involvement of numerous team members, the management of patients will require coordinated communication and understanding of the roles of each member of the study team. Be sure to identify all team members and to notify the NIH of any changes in personnel.

Each transplant center will have one Principal Investigator (PI), and may or may not also have a Co-Principal Investigator (Co-PI). The PI and Co-PI will also serve as one of the team members outlined below.

### 6.1 MEMBERS

#### 6.1.1 Kidney Transplant Centers

Transplant centers that are transplanting kidney patients in this study will have the following team members (one also being the PI):

- Kidney transplant surgeon
- HIV physician
- Nephrologist
- Study coordinator

#### 6.1.2 Liver Transplant Centers

Transplant centers that are transplanting liver patients in this study will have the following team members (one also being the PI):

- Liver transplant surgeon
- HIV physician
- Hepatologist
- Study coordinator

#### 6.1.3 Kidney and Liver Transplant Centers

Transplant centers who are transplanting kidney and liver patients in this study will have all of the above team members. One team member may serve the same role for each organ (i.e. the HIV physician may be the same person for both kidney and liver patients) or there may be two different members.

#### 6.1.4 Pediatric Transplant Centers

Because we do not expect to enroll many pediatric patients in this study, and because of limited funding in adding pediatric team members, we have set up a referral system for pediatric patients and have several centers performing pediatric transplants. These centers must identify:

- Pediatric transplant surgeon for each organ
- Pediatric HIV physician(s)
- Pediatric Nephrologist (if transplanting pediatric kidney patients)
- Pediatric Hepatologist (if transplanting pediatric liver patients)

## **6.2 ROLE OF THE PRINCIPAL INVESTIGATOR**

The responsibilities of the designated PI, who is a physician with substantial experience in the performance of clinical trials, will include:

- Supervise the site registration process
- Direct the activities of the team
- Coordinate the scientific and administrative operations of the center
- Ensure adherence by personnel to the procedures described in and required by the Protocol.
- Insure that updates and modifications are added to the Protocol and Consent forms as the NIH and UCSF send them. Also insure proper IRB amendments and renewals are prepared and approved.
- Spend sufficient time to adequately observe study procedures
- Assure fiscal responsibility in the disposition of study funds

## **6.3 ROLE OF THE STUDY COORDINATOR**

The study coordinator is responsible for supervising day-to-day operation in the study unit and serves as the primary contact for the study patients and for the Project Managers and Data Management center (EMMES). The duties of the study coordinator are to:

- Ensure that potential patients receive appropriate information about the study, including information sheets and informed consent statements
- Register patients in the study (using the EMMES database)
- Schedule patient appointments
- Notify the NIH Project Manager of changes or impending changes in the personnel, address, and telephone numbers of the study team
- Maintain a calendar of patient visits, meetings, scheduled telephone calls, or visits from the Protocol Monitor
- Obtain necessary information about deceased patients (e.g., death certificates)
- Maintain an inventory of medications or supplies needed
- Along with the PI, Add updates sent by NIH and UCSF to the Protocol, Consents, and Manual of Operations
- Check completed data forms for accuracy and completeness
- Submit complete data to the EMMES corporation, NIH, and UCSF in a timely manner
- Respond to data queries from the EMMES corporation
- Other duties as defined by the Steering Committee or Data and Safety Monitoring Board (DSMB)

## **7 SUBJECT SELECTION AND ENROLLMENT**

---

### **7.1 ELIGIBILITY SCREENING**

When a patient begins screening for the study, distribute the IRB approved information sheets titled “Eligibility Criteria” and “Primary Medical Care Provider Procedures Before Transplantation” to the patient.

The “Eligibility Criteria” information sheet outlines the inclusion and exclusion criteria for the patient. The “Primary Medical Care Provider Procedures Before Transplantation” information sheet outlines certain additional tests and procedures that need to be performed by the patient’s primary medical care provider (in addition to procedures done at the transplant center) in order to determine eligibility to be in the study. The results of these tests and procedures should be faxed to the study coordinator by the patient’s primary medical care provider so that the team can decide if the patient should be in this study.

### **7.2 SCREENING AND ENROLLMENT LOG**

For all patients that sign the pre-enrollment consent or the study consent, please register in the pre-enrollment segment portion of the database at EMMES. Separate instructions have been provided to each site regarding the online screen log. Contact the data manager at EMMES for further information or questions with the data entry system (see chapter 3 for contact information).

### **7.3 ENROLLMENT PROCEDURES**

#### **7.3.1 Pre-Transplant**

If a patient has been screened and meets study eligibility criteria, the following steps should be taken:

1. The plan of the study should be reviewed with the patient and any questions by the patient should be answered.
2. The patient should be asked to sign the Informed Consent document.
3. Once the patient signs the Informed Consent, the patient should be enrolled in the pre-transplant phase of the study and assigned a participant ID using the EMMES Internet Data Entry System (IDES) at [www.emmes.com](http://www.emmes.com).
4. Patients enrolled in the pre-transplant phase of the study will be followed every three months. Every three months, the patient’s primary medical care provider will be required to fax to the study coordinator the patients CD4+ T-cell count and HIV-1 RNA. In addition, liver patients will also be required to send Creatinine, Total Bilirubin, and INR information every three months. This data is to be entered into the EMMES IDES so that the patient’s continued eligibility can be monitored.

5. Any interval opportunistic complications should also be recorded on the appropriate case report forms.
6. If the subject is no longer eligible for transplant, or for the study, or wishes to withdraw from the study, the reason(s) should be recorded on the appropriate case report form using the EMMES IDES.
7. Eligibility at the time of organ availability will be determined based on an eligible CD4+ T-cell count at least once in the 16 weeks prior to transplant, and the most recent viral load result no more than 16 weeks prior to transplant. These results will be collected from the primary care provider and entered into the data management system every 12 weeks.

### **7.3.2 Post-Transplant**

Using the EMMES IDES, enroll the patient into the post-transplant phase of the study. It is important to enroll the patient on the DAY OF the transplant since the EMMES IDES will assume that the date of actual database enrollment is the date of transplant, and all calendars and schedules created by the EMMES IDES will be generated from that date.

### **7.4 COMBINED LIVER/KIDNEY TRANSPLANTS**

Patients requiring a combined liver/kidney transplant will need to sign both consent forms. When enrolling these patients into the EMMES IDES, you will note that this is a combined liver/kidney transplant patient. The appropriate case report forms will then be available to you. This should not happen often. We will work with you to adjust blood volumes for storage so that all required labs for both organs can be sent (almost all of these are the same for both organs).

### **7.5 RETRANSPLANT**

Transplant failures should continue study follow-up on their initial schedule unless the patient expires or revoked consent. Adverse events would not need to be recorded (only SAEs would require reporting). In addition, only the Visit Documentation and Infectious and Neoplastic Complications Tracking Forms would be required every 6 months, as well as recording of HIV VL and CD4 count every 6 months. A paper copy of the Transplant Report Form should be filled out for each re-transplant and faxed to the EMMES Data Manager.

## 8 DATA COLLECTION

---

Case report forms will be completed electronically using the EMMES Internet Data Entry System (IDES). Please refer to the EMMES IDES User's Guide located at [www.emmes.com](http://www.emmes.com) for complete details on completing the case report forms.

## 9 CLINICAL MANAGEMENT PROTOCOLS

---

### 9.1 USE OF INVESTIGATIONAL DRUGS

The use of investigational medications post-transplant is not recommended. No investigational medications will be given to subjects participating in this study post-transplant without prior approval from the Operations Committee.

### 9.2 SPECIAL CONSIDERATIONS FOR CHILDREN

All medications will be dose adjusted for pediatric use. Medication doses should be determined based upon standard of care for pediatric dosing.

### 9.3 IMMUNOSUPPRESSION: RECOMMENDED REGIMENS

#### 9.3.1 Calcineurin Inhibitor

Cyclosporine dosing should be initiated as follows:

- When used with a PI-containing regimen: 25 – 50 mg PO BID. This also applies to combined PI-NNRTI-based regimens
- When used with an NNRTI-containing regimen: 200 – 450 mg PO BID (200 mg if on Nevirapine; 250 – 250 mg if on Efavirenz)

Tacrolimus dosing should be initiated as follows:

- When used with a PI-containing regimen: 1 mg PO once to twice per week. This also applies to combined PI-NNRTI-based regimens
- When used with an NNRTI-containing regimen: 1 - 2 mg bid PO

Modifications for toxicity: should be made at the discretion of the study team.

#### 9.3.2 Mycophenolate mofetil (Cellcept)

Standard dosing (1000 mg PO BID) will be initiated in all kidney and liver subjects. Dosing should be modified based on toxicity (neutropenia, GI) and clinical judgment. MMF may be tapered in stable liver transplant recipients after 6 months of therapy.

### 9.4 OPPORTUNISTIC INFECTION PROPHYLAXIS: RECOMMENDED REGIMENS

#### 9.4.1 Pneumocystis Carinii Pneumonia (PCP)

##### 9.4.1.1 Primary Prophylaxis (Patients with No Prior History of PCP)

Regimen:

Preferred: bactrim 1 double strength tablet (160 mg trimethoprim/800 mg sulfamethoxazole) PO daily or bactrim 1 single strength tablet (80 mg trimethoprim/400 mg sulfamethoxazole) PO daily.

Alternatives: bactrim DS 1 tab PO TIW or dapsone 100 mg PO QD (dapsone contraindicated if G6PD deficient).

If bactrim and dapsone allergic (or G6PD deficient), consider atovaquone 1500 mg PO daily or aerosolized pentamidine 300 mg via respigard II nebulizer monthly.

Strategies for managing mild reactions to bactrim include discontinuation of the drug and resuming it at a lower dose or re-challenging with gradual dose escalation. Bactrim suspension for dose escalation (8 mg trimethoprim/40 mg sulfamethoxazole) 1 cc PO QD x 3d, 2cc PO QD x 3d, 5 cc PO QD x 3d, 1 single strength PO QD.

#### 9.4.1.2 *Secondary Prophylaxis (Patients with a Prior History of PCP)*

Regimen:

See section 9.4.1.1.

### 9.4.2 **Toxoplasmosis**

#### 9.4.2.1 *Primary Prophylaxis (Patients with No Prior History of Toxoplasmosis)*

Regimen:

Preferred: bactrim DS 1 tab PO QD.

Alternatives:

- bactrim SS 1 tab PO QD
- dapsone 100 mg PO daily + pyrimethamine 50 mg PO QD + leucovorin 25 mg PO QD, or
- atovaquone 1500 mg PO QD

#### 9.4.2.2 *Secondary Prophylaxis (Patients with a Prior History of Toxoplasmosis)*

Regimen:

Preferred: pyrimethamine 25 mg PO QD plus sulfadiazine 100 mg/kg PO QD plus leucovorin 25 mg PO QD. Separate PCP prophylaxis should be discontinued if this regimen is used.

Alternative: for patients who cannot tolerate sulfa drugs pyrimethamine 25 mg PO QD plus clindamycin 300 mg PO QID. Note that only the combination of pyrimethamine plus sulfadiazine appears to provide protection against PCP, thus PCP prophylaxis must be continued with this regimen.

### 9.4.3 **Mycobacterium Avium Complex (MAC)**

#### 9.4.3.1 *Primary Prophylaxis (Patients with No Prior History of MAC)*

Regimen:

Preferred: azithromycin 1200 mg PO weekly

Alternative:

- clarithromycin 500 mg PO BID, although drug interactions with immunosuppressive agents must be considered.
- Because of the risk of rejection due to drug interaction with calcineurin inhibitors, rifabutin and rifampin should be avoided for prophylaxis unless all other alternatives have been exhausted. If unable to tolerate a macrolide, consider rifabutin 300 mg PO QD. Rifabutin must be administered at one-half the usual daily dose (i.e., reduce from 300 mg to 150 mg PO QD) with protease inhibitors. Rifabutin should not be used with the protease inhibitor hard-gel saquinavir when it is used as a single protease inhibitor (acceptable if used in combination with ritonavir) or the nonnucleoside reverse transcriptase inhibitor delavirdine. Information is lacking regarding co-administration of rifabutin with soft-gel saquinavir or nevirapine.

#### 9.4.3.2 *Secondary Prophylaxis (Patients with a Prior History of MAC)*

Regimen:

Preferred: azithromycin 600 mg PO QD in combination with ethambutol 15 mg/kg/day. Regimen may be modified based on previous MAC treatment.

Alternative: clarithromycin 500 mg PO BID plus ethambutol 15 mg/kg/day (drug interactions with immunosuppressive agents must be considered). Because of the risk of rejection due to drug interaction with calcineurin inhibitors, rifabutin and rifampin should be avoided for prophylaxis unless all other alternatives have been exhausted.

#### 9.4.4 **Cytomegalovirus (CMV)**

##### 9.4.4.1 *Primary Prophylaxis (Patients with No Prior History of CMV)*

Regimen:

Per site practice as long as this is within the generally accepted standard of care.

##### 9.4.4.2 *Secondary Prophylaxis (Patients with a Prior History of CMV)*

Regimen:

Preferred: valganciclovir 900 mg PO QD

Alternative: ganciclovir 1 gr PO TID

#### 9.4.5 **Epstein Barr Virus (EBV)**

##### 9.4.5.1 *Primary Prophylaxis for EBV*

Regimen:

Ganciclovir 5 mg/kg IV QD while hospitalized then change to ganciclovir 1 gram PO TID x 1 year. Patients should not be continued on acyclovir if they are on ganciclovir.

#### **9.4.6 Cryptococcosis, extrapulmonary**

##### *9.4.6.1 Primary Prophylaxis (Patients with No Prior History of Cryptococcosis)*

Regimen:

None Recommended

##### *9.4.6.2 Secondary Prophylaxis (Patients with a Prior History of Cryptococcosis)*

Regimen:

Preferred: fluconazole 200 mg PO QD.

Severe toxicity from calcineurin inhibitors may result if daily fluconazole or another azole antifungal agent is combined with calcineurin inhibitors or protease inhibitors and levels must be monitored closely. At a minimum, the dose of calcineurin inhibitors should be reduced by 50%, but the amount is variable and sometimes more significant dose reduction is required. Daily calcineurin inhibitor trough levels should be monitored during the first week of therapy, or longer if necessary. Similar adjustments are required in the dosing of sirolimus and tacrolimus.

#### **9.4.7 Histoplasmosis**

##### *9.4.7.1 Primary Prophylaxis (Patients with No Prior History of Histoplasmosis)*

Regimen:

None recommended.

##### *9.4.7.2 Secondary Prophylaxis (Patients with a Prior History of Histoplasmosis)*

Regimen:

Preferred: itraconazole 200 mg PO BID taken with food

Alternative: fluconazole 400 mg PO QD. Severe toxicity from calcineurin inhibitors may result if daily fluconazole is combined with calcineurin inhibitors and levels must be monitored closely.

Severe toxicity from calcineurin inhibitors may result if daily fluconazole or another azole antifungal agent is combined with calcineurin inhibitors or protease inhibitors and levels must be monitored closely. At a minimum, the dose of calcineurin inhibitors should be reduced by 50%, but the amount is variable and sometimes more significant dose reduction is required. Daily calcineurin inhibitor trough levels should be monitored during the first week of therapy, or longer if necessary. Similar adjustments are required in the dosing of sirolimus and tacrolimus.

### **9.5 OPPORTUNISTIC INFECTION MONITORING GUIDELINES**

#### **9.5.1 CMV**

Retinitis is the major manifestation of HIV-associated CMV end-organ disease. This is a sight threatening disorder. Floaters and peripheral visual defects are

common but may not be present, thus screening is standard of care in HIV-infected patients with CD4 counts < 50. Thus, any newly CMV viremic subject should have an ophthalmologic dilated fundoscopic examination within 3 - 7 days, or immediately if any visual symptoms including floaters or peripheral visual defects are present.

## 9.6 TB PROPHYLAXIS: RECOMMENDED REGIMENS

### Regimen:

#### Preferred:

- INH 300 mg PO QD + pyridoxine 50 mg PO QD x 9 months or
- INH 900 mg + pyridoxine 100 mg BIW x 9 months

#### For children:

INH 10-15 mg/kg/PO day (max 300mg PO ) x 1month + pyridoxine 1-2mg/kg/PO day (max 50 mg PO QD) x 9 months

Alternatives: to be considered only if absolute contraindications to INH regimens. Because of the risk of rejection due to drug interaction with calcineurin inhibitors, rifabutin and rifampin should be avoided for prophylaxis unless all other alternatives have been exhausted.

- Rifampin 600 mg PO QD x 4 months
- Rifabutin 300 mg PO QD
- x 4 months (no data are available on this possible regimen to be used with a protease inhibitor; monitor for uveitis)

For children: INH 20-30 mg/kg BIW + Pyridoxine 2-4 mg/kg (max 100mg)  
Rifampin 10-20 mg/kg/day (max 600mg) x 6 months (only for INH resistant MTB)

Rifampin should not be administered with protease inhibitors or nonnucleoside reverse transcriptase inhibitors. Rifabutin can be administered at one-half the usual daily dose (i.e., reduce from 300 mg to 150 mg qd) with nelfinavir, indinavir and amprenavir. Rifabutin should not be used with the protease inhibitor hard-gel saquinavir when it is used as a single protease inhibitor (acceptable if used in combination with ritonavir) or the nonnucleoside reverse transcriptase inhibitor delavirdine. Information is lacking regarding co-administration of rifabutin with soft-gel saquinavir or nevirapine.

## 9.7 SPECIAL CONSIDERATIONS WITH ANTIRETROVIRALS

### 9.7.1 Mycophenolate mofetil and Nucleoside Analogues

*In vitro* studies demonstrate the following interaction between Mycophenolate mofetil (MMF) and nucleoside analogue reverse transcriptase inhibitors (NRTIs): antagonism with zidovudine (AZT) and stavudine (D4T), synergy with abacavir and didanosine (ddl), and no effect with epivir (3TC). Attempts will be made to minimize the use of zidovudine and stavudine in subjects who are using MMF. In some cases, based on tolerance, resistance, or other issues, these agents may still be used.

### 9.7.2 Nevirapine

For liver transplant candidates on nevirapine, may reduce dose from 200 mg bid to 200 mg qD for the first 2 weeks post-transplant, then resume 200 mg bid.

Because of the potential for acute hepatic necrosis with Viramune (nevirapine), attempts will be made to minimize the use of this drug when reasonable alternatives are available.

### 9.7.3 Didanosine Co-administered with Ribavirin

Co-Administration of ribavirin with didanosine should be undertaken with caution, and patients should be monitored closely for didanosine-related toxicities. Didanosine should be suspended if signs or symptoms of pancreatitis, symptomatic hyperlactatemia, or lactic acidosis develop.

### 9.7.4 Didanosine Co-administered with Tenofovir

Pharmacokinetic data demonstrate that co-administration of tenofovir and didanosine resulted in significant increases in didanosine exposures. Co-administration of tenofovir and didanosine should be undertaken with caution, and patients should be monitored closely for didanosine-related toxicities. Didanosine should be suspended if signs or symptoms of pancreatitis, symptomatic hyperlactatemia, or lactic acidosis develop.

For patients > 60kg, Videx-EC (didanosine) 250mg QD. No data are available for patients <60kg (consider 125 mg QD).

### 9.7.5 ARV drug interactions

New interactions are rapidly identified in the field of ARV pharmacokinetics (examples: SQV should not be used with NNRTIs without RTV; LPV/r dose should be increased when combined with NNRTI, etc). Any questions about combination therapy should be directed to Michelle Roland at the University of California, San Francisco. See section 2 for contact information.

### 9.7.6 Pregnancy

Specific guidelines for pregnancy prevention should be followed according to the agents in use. Note that some ARVs lower plasma levels of oral contraceptive pills and render them ineffective. A barrier method is always recommended and is required in the study.

Use in pregnancy Categories for Antiretrovirals:

Category	Description
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus, however, there are no adequate and well-controlled studies in pregnant women.

	<b>or</b> Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. <b>or</b> No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant

Antiretroviral Drug	FDA Pregnancy Category
Zidovudine	C
Zalcitabine	C
Didanosine	B
Stavudine	C
Lamivudine	C
abacavir	C
Saquinavir	B
Indinavir	C
Ritonavir	B
Nelfinavir	B
amprenivir	C
Lopinavir/ritonavir	C
Nevirapine	C
Delavirdine	C
efavirenz	C

**9.8 ANTIRETROVIRAL DOSE ADJUSTMENTS FOR HEPATIC AND RENAL INSUFFICIENCY**

Generic (Trade) Names	Daily Dose	Dosing in Renal Insufficiency	Dosing in Hepatic Impairment												
<b>Nucleoside Reverse Transcriptase Inhibitors</b>															
<b>Abacavir (Ziagen)</b>	300 mg PO BID	No need for dosage adjustment	No dosage recommendation												
<b>Didanosine (Videx )</b>	<p><u>&gt; 60 kg</u> 400 mg PO qd</p> <p><u>&lt; 60 kg</u> 250mg qd</p>	<p><u>Dose/day</u></p> <table border="1"> <thead> <tr> <th><u>CrCl (mL/min)</u></th> <th><u>&gt; 60 kg</u></th> <th><u>&lt; 60 kg</u></th> </tr> </thead> <tbody> <tr> <td>30-59</td> <td>200 mg</td> <td>125 mg</td> </tr> <tr> <td>10-29</td> <td>125 mg</td> <td>100 mg</td> </tr> <tr> <td>&lt; 10</td> <td>125 mg</td> <td>75 mg</td> </tr> </tbody> </table> <p><b>CAPD or hemodialysis patients: use same dose as CrCl &lt; 10 mL/min</b></p>	<u>CrCl (mL/min)</u>	<u>&gt; 60 kg</u>	<u>&lt; 60 kg</u>	30-59	200 mg	125 mg	10-29	125 mg	100 mg	< 10	125 mg	75 mg	No dosage recommendation
<u>CrCl (mL/min)</u>	<u>&gt; 60 kg</u>	<u>&lt; 60 kg</u>													
30-59	200 mg	125 mg													
10-29	125 mg	100 mg													
< 10	125 mg	75 mg													
<b>Emtricitabine (Emtriva)</b>	200 mg PO qd	<table border="1"> <thead> <tr> <th><u>CrCl (mL/min)</u></th> <th><u>Dose</u></th> </tr> </thead> <tbody> <tr> <td>30-49</td> <td>200 mg q48h</td> </tr> <tr> <td>15-29</td> <td>200 mg q72h</td> </tr> <tr> <td>&lt; 15</td> <td>200 mg q96h</td> </tr> </tbody> </table> <p><b>Hemodialysis patients: 200 mg q96h (dose after dialysis if dose is due on dialysis day)</b></p>	<u>CrCl (mL/min)</u>	<u>Dose</u>	30-49	200 mg q48h	15-29	200 mg q72h	< 15	200 mg q96h	No dosage recommendation				
<u>CrCl (mL/min)</u>	<u>Dose</u>														
30-49	200 mg q48h														
15-29	200 mg q72h														
< 15	200 mg q96h														
<b>Lamivudine (Epivir )</b>	300 mg PO qd or 150mg PO BID	<table border="1"> <thead> <tr> <th><u>CrCl (mL/min)</u></th> <th><u>Dose</u></th> </tr> </thead> <tbody> <tr> <td>30-49</td> <td>150 mg qd</td> </tr> <tr> <td>15-29</td> <td>150 mg x</td> </tr> </tbody> </table>	<u>CrCl (mL/min)</u>	<u>Dose</u>	30-49	150 mg qd	15-29	150 mg x	No dosage recommendation						
<u>CrCl (mL/min)</u>	<u>Dose</u>														
30-49	150 mg qd														
15-29	150 mg x														

		<p>1, then 100 mg qd</p> <p>5-14 150 mg x 1, then 50 mg qd</p> <p>&lt; 5 150 mg x 1, then 25 mg qd</p> <p>No data on hemodialysis</p>											
<b>Stavudine (Zerit )</b>	<p><u>&gt; 60 kg</u> 40 mg PO BID</p> <p><u>&lt; 60 kg</u> 30 mg PO BID</p>	<p><u>Dose</u></p> <table> <thead> <tr> <th><u>CrCl (mL/min)</u></th> <th><u>&gt; 60 kg</u></th> <th><u>&lt; 60 kg</u></th> </tr> </thead> <tbody> <tr> <td>26-50</td> <td>20 mg q12h</td> <td>15 mg q12h</td> </tr> <tr> <td>10-25</td> <td>20 mg q24h</td> <td>15 mg q24h</td> </tr> </tbody> </table> <p><b>Hemodialysis - same dose as CrCl 10-25 mL/min, dose after dialysis on day of dialysis</b></p>	<u>CrCl (mL/min)</u>	<u>&gt; 60 kg</u>	<u>&lt; 60 kg</u>	26-50	20 mg q12h	15 mg q12h	10-25	20 mg q24h	15 mg q24h	No dosage recommendation	
<u>CrCl (mL/min)</u>	<u>&gt; 60 kg</u>	<u>&lt; 60 kg</u>											
26-50	20 mg q12h	15 mg q12h											
10-25	20 mg q24h	15 mg q24h											
<b>Tenofovir (Viread)</b>	300 mg PO qd	<table> <thead> <tr> <th><u>CrCl (mL/min)</u></th> <th><u>Dose</u></th> </tr> </thead> <tbody> <tr> <td>&gt; 50</td> <td>300 mg qd</td> </tr> <tr> <td>30-49</td> <td>300 mg q48h</td> </tr> <tr> <td>10-29</td> <td>300 mg biw</td> </tr> <tr> <td>ESRD</td> <td>300 mg q wk</td> </tr> </tbody> </table>	<u>CrCl (mL/min)</u>	<u>Dose</u>	> 50	300 mg qd	30-49	300 mg q48h	10-29	300 mg biw	ESRD	300 mg q wk	No dosage recommendation
<u>CrCl (mL/min)</u>	<u>Dose</u>												
> 50	300 mg qd												
30-49	300 mg q48h												
10-29	300 mg biw												
ESRD	300 mg q wk												
<b>Zalcitabine (Hivid)</b>	0.75 mg PO TID	<table> <thead> <tr> <th><u>CrCl (mL/min)</u></th> <th><u>Dose</u></th> </tr> </thead> <tbody> <tr> <td>10-40</td> <td>0.75 mg BID</td> </tr> <tr> <td>&lt; 10</td> <td>0.75 mg qd</td> </tr> </tbody> </table>	<u>CrCl (mL/min)</u>	<u>Dose</u>	10-40	0.75 mg BID	< 10	0.75 mg qd	No dosage recommendation				
<u>CrCl (mL/min)</u>	<u>Dose</u>												
10-40	0.75 mg BID												
< 10	0.75 mg qd												

		No data on hemodialysis							
<b>Zidovudine (Retrovir)</b>	300 mg PO BID	"Severe" renal impairment or hemodialysis - 100mg TID	No dosage recommendation						
<b>Non- Nucleoside Reverse Transcriptase Inhibitors</b>									
<b>Delavirdine (Rescriptor)</b>	400 mg PO TID	No dosage adjustment necessary	No recommendation; use with caution in patients with hepatic impairment						
<b>Efavirenz (Sustiva<sup>®</sup>)</b>	600 mg PO qd	No dosage adjustment necessary	No recommendation; use with caution in patients with hepatic impairment						
<b>Nevirapine (Viramune)</b>	200 mg PO BID	No dosage adjustment necessary	No data available; avoid use in patients with moderate to severe hepatic impairment						
<b>Protease Inhibitors</b>									
<b>Amprenavir (Agenerase)</b>	1,200 mg PO BID	No dosage adjustment necessary	<table border="0"> <thead> <tr> <th><u>Child-Pugh Score</u></th> <th><u>Dose</u></th> </tr> </thead> <tbody> <tr> <td>5-8</td> <td>450 mg BID</td> </tr> <tr> <td>9-12</td> <td>300 mg BID</td> </tr> </tbody> </table>	<u>Child-Pugh Score</u>	<u>Dose</u>	5-8	450 mg BID	9-12	300 mg BID
<u>Child-Pugh Score</u>	<u>Dose</u>								
5-8	450 mg BID								
9-12	300 mg BID								
<b>Atazanavir (Reyataz)</b>	400 mg PO qd	No dosage adjustment necessary	<table border="0"> <thead> <tr> <th><u>Child-Pugh Score</u></th> <th><u>Dose</u></th> </tr> </thead> <tbody> <tr> <td>Class B</td> <td>300 mg qd</td> </tr> <tr> <td>Class C</td> <td>not recommended</td> </tr> </tbody> </table>	<u>Child-Pugh Score</u>	<u>Dose</u>	Class B	300 mg qd	Class C	not recommended
<u>Child-Pugh Score</u>	<u>Dose</u>								
Class B	300 mg qd								
Class C	not recommended								
<b>Fosamprenavir (Lexiva)</b>	1,400 mg PO BID	No dosage adjustment necessary	<table border="0"> <thead> <tr> <th><u>Child-Pugh</u></th> <th><u>Dose</u></th> </tr> </thead> <tbody> <tr> <td></td> <td></td> </tr> </tbody> </table>	<u>Child-Pugh</u>	<u>Dose</u>				
<u>Child-Pugh</u>	<u>Dose</u>								

			<u>Score</u> 5-8 700 mg BID 9-12 not recommended  Ritonavir boosting should not be used in patients with hepatic impairment
<b>Indinavir (Crixivan)</b>	800 mg PO q8h	No dosage adjustment necessary	<b><u>Mild to moderate hepatic insufficiency due to cirrhosis;</u></b> 600 mg q8h
<b>Lopinavir/ritonavir (Kaletra)</b>	400 mg/100 mg PO BID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
<b>Nelfinavir (Viracep®)</b>	1,250 mg PO BID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
<b>Ritonavir (Norvir)</b>	600 mg PO BID	No dosage adjustment necessary	No dosage adjustment in mild hepatic impairment; no data for moderate to severe impairment, use with caution
<b>Saquinavir soft gel cap (Fortovase)</b>	1,200 mg TID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
<b>Fusion Inhibitors</b>			
<b>Enfuvirtide (Fuzeon)</b>	90 mg SQ q12h	No dosage adjustment necessary	No dosage recommendation

\* Combination products of Combivir and Trizivir should not be used in patients with renal insufficiency

## 9.9 HBV AND HBIG THERAPY

Patients who test HepB core Ab+ and HepSAg-/HepBSAb- will need to have an HBV DNA and HBV EA<sub>g</sub> done in order to confirm HBV infection. If either marker is positive, repeat test to rule out false positives. If confirmed, treat with HBIG as outlined in the protocol for SA<sub>g</sub>+ patients. If undetectable, do not start HBIG therapy.

## 9.10 BIOPSY GUIDELINES FOR BLEEDING DISORDERS

### 9.10.1 Indications and Safety Considerations

Individuals with bleeding disorders may be at increased risk for bleeding when undergoing liver biopsy. This may relate to the underlying coagulation factor deficiency or other coagulopathies, such as the coagulopathy associated with liver disease, drugs, renal dysfunction, or other condition. For this reason, individuals with hemophilia should be evaluated by hematologists with expertise in coagulation disorders prior to undergoing a liver biopsy.

The evaluation prior to liver biopsy should include obtaining preoperative screening tests including prothrombin time (PT), platelet count, and inhibitor titer. In addition, information regarding past hepatitis and liver function tests, which are obtained as part of comprehensive hemophilia care, should be obtained. A list of current medications should be determined, with specific attention to drugs that may cause Vitamin K deficiency or platelet dysfunction, which may enhance bleeding tendency in the patient with hemophilia. Concomitant coagulopathies that may increase bleeding risk, including the presence of portal hypertension with thrombocytopenia, Vitamin K deficiency, or analgesics causing platelet dysfunction should be assessed.

Specific safety considerations include the correction of any concomitant coagulopathy prior to the liver biopsy procedure, for example, discontinuing nonsteroidal anti-inflammatory agents or correction of Vitamin K deficiency. In addition, consideration should be given to the less invasive transjugular biopsy technique<sup>6</sup>, which is associated with a lower bleeding risk<sup>82</sup>. The hematologist should seek information regarding the potential for transjugular biopsy and the safety record with this procedure at the institution and discuss this information with the patient to assist in decision-making. Finally, consideration should be made regarding whether information from the biopsy will affect treatment or long-term management.

### 9.10.2 Liver Biopsy (Percutaneous or Transjugular)

1. Review the patient's medication list for medications which may enhance bleeding tendency, e.g. nonsteroidal anti-inflammatory agents, and where possible discontinue such agents.
2. Check the prothrombin time (PT) and platelet count prior to the procedure.
3. Give Vitamin K and platelets preoperatively as needed to correct the PT and platelet count towards normal. This may require several days for optimal correction.

4. Immediately prior to the procedure, that is, within 5-10 minutes of the procedure, infuse clotting factor to correct the factor level to 100%. If platelets and plasma are required prior to the procedure, they should precede the factor infusion.
5. Draw a PTT at 10 to 15 minutes after the infusion for baseline and help with future management.
6. Following the procedure, obtain the volume of blood loss during the procedure, and order a hemoglobin and hematocrit.
7. Factor replacement may be continued at a 50% dose 8-12 hours and again at 24 hours later. For those undergoing percutaneous biopsy, dosing may be continued for up to 3-5 days or more, at the physician's discretion.
8. Additional doses of Vitamin K and plasma may be given at the physician's discretion. If the vital signs and hemoglobin and hematocrit are stable, if the patient is able to receive factor treatment reliably as an outpatient, and if close follow-up with the physician is possible, the patient may be discharged, at the physician's discretion.

### 9.10.3 Kidney Biopsy

For those undergoing kidney biopsy, management of hemeostasis should be as outlined in 8.1.2 above.

### 9.11 DIGITAL RECTAL EXAM

Both HIV-infected individuals and solid organ transplant recipients are at increased risk for HPV-associated cancers. HIV-positive patients have a high prevalence of anogenital human papillomavirus (HPV) infection and anal cancer precursors, known as anal intraepithelial neoplasia (AIN) 2 or 3. Therefore, HIV-positive transplant patients may be at especially high risk of anal cancer. Since HIV-positive solid organ transplant patients are at risk for anal cancer, it is recommended that, at a minimum, all subjects receive routine digital rectal exams (DRE) to screen for rectal cancers.

### 9.12 GUIDELINES FOR REPEATING SEROLOGIES

CMV Ab <sup>6</sup>	Repeat if not previously positive
HepBSAg <sup>6</sup>	Repeat if both HepBSAg and HepBSAb were previously negative. <b>HOWEVER</b> , if post liver transplant, always repeat.
HepBSAb <sup>6</sup>	Repeat if both HepBSAg and HepBSAb were previously negative. <b>HOWEVER</b> , if post liver transplant, always repeat and obtain anti-HBs titer.
HepB core Ab <sup>6</sup>	Repeat if HepBSAg, HepBSAb, and HepB Core Ab were all previously negative
HepB DNA (only if HepBSAg+)	Always repeat if HepBSAg positive

HbeAg (only if HepBSAg+)	Repeat if HepBSAg positive, only up to time of LT, then stop.
Anti-Hbe (only if HepBSAg+)	Repeat if HepBSAg positive, only up to time of LT, then stop.
Anti-HDV (only if HepBSAg+)	Only needed once pre-transplant. If not done pre-transplant, do one post transplant.
HCV Ab <sup>6</sup>	Repeat if not previously positive
HCV RNA (only if HCV Ab+)	Always repeat if HCV Ab positive
EBV Ab <sup>6</sup>	Repeat if not previously positive. (Note: EBV IgG + = past infection; EBV IgM + = recent infection)

## **10 STUDY VISIT SCHEDULE AND SPECIMENS**

---

### **10.1 TIMING OF EVALUATIONS**

#### **10.1.1 Screening and Pre-Entry Evaluations**

Screening evaluation for eligibility will occur prior to transplantation. Screening evaluations to determine eligibility may be completed at any time after transplant eligibility is determined. Screening tests indicated on the schedule of events (footnote 3) must be completed no more than 12 months prior to transplantation. All others only need to be completed once, regardless of timing of screening, unless otherwise indicated in the schedule of events. CD4 and HIV RNA testing will be recorded every 12 weeks and must be completed within 16 weeks of transplantation. Pre-transplant study enrollment of eligible subjects will occur once all screening labs have been completed and the informed consent has been signed.

For sub-studies requiring blood to be collected and shipped for sub-study analysis (including HCV sub study, HBV sub study, and all other cluster specific sub studies and blood for storage), the pre-transplant blood draw should not be taken during the initial screening phase. These specimens should be collected at anytime pre-transplant once the patient is nearing transplant, and may also be drawn on the day of the transplant as long as they are drawn pre-transplant.

#### **10.1.2 On-Study Evaluations**

Once patient has been transplanted, study related visits will occur at day 0, weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 26, 36, 44, and 52, every 3 months in years 2 and 3, and every 6 months in years 4 and 5. Although it is preferred that all study visits occur at the transplant center, only the weeks 12, 26, 52, and year 2 study visits must occur at the transplant center. If the patient is unable to return to the transplant center for any other post-transplant study visits, a complete medical review should be conducted by telephone. In addition, all necessary lab work as outlined in the schedule of events should be performed locally with the results faxed to the transplant center for data entry.

#### **10.1.3 Study Discontinuation Evaluation**

Patients who register for this study and withdraw their consent prior to transplant will be terminated from this study with no additional follow-up necessary.

### **10.2 VISIT NUMBERS**

Visit 00 = pre  
Visit 01 = day 0 or day of transplant  
Visit 02 = week 1  
Visit 03 = week 2  
Visit 04 = week 4  
Visit 05 = week 6  
Visit 06 = week 8  
Visit 07 = week 10  
Visit 08 = week 12

Visit 09 = week 16  
Visit 10 = week 20  
Visit 11 = week 26  
Visit 12 = week 36  
Visit 13 = week 44  
Visit 14 = week 52  
Visit 15 = week 65  
Visit 16 = Week 78  
Visit 17 = week 91  
Visit 18 = week 104 or year 2  
Visit 19 = week 117  
Visit 20 = week 130  
Visit 21 = week 143  
Visit 22 = week 156 or year 3  
Visit 23 = week 182  
Visit 24 = week 208 or year 4  
Visit 25 = week 234  
Visit 26 = week 260 or year 5

### **10.3 VISIT WINDOW**

Attempts should be made to complete study visits as close as possible to the defined study visit date. Study visits may occur within 2 weeks prior to the defined visit time point. Study visits may occur after the defined study visit time point up to the mid-way point between the target date of the study visit and the subsequent study visit. For example, week 26 visit may occur up to week 31 [eg  $26 + (36 - 26)/2 = 31$ ].

### **10.4 STUDY VISITS FOR PATIENTS WITH GRAFT FAILURE**

Patients who experience graft failure will be followed using the same schedule unless the patient expires or revoked consent. Adverse events would not need to be recorded (only SAEs would require reporting). In addition, only the Visit Documentation and Infectious and Neoplastic Complications Tracking Forms would be required every 6 months, as well as recording of HIV VL and CD4 count every 6 months. A paper copy of the Transplant Report Form should be filled out for each retransplant and faxed to the EMMES Data Manager.

### **10.5 TRANSPLANTATION AND FOLLOW-UP AT DIFFERENT CENTERS**

Subjects may be transplanted at one HIVTR Transplant Center and then followed at another HIVTR Transplant Center if both Institutions and Principal Investigators agree. This agreement needs to be documented at both centers within the HIVTR records and available for review. This situation might occur if the waiting time at one center is much shorter than the referring centers waiting time, and subjects may find it easier to return for follow-up at the referring center.

These subjects would be enrolled and registered at the original referring center performing the post-transplant follow-up. The center performing the transplant would be required to fax any source documentation to the referring center for timely data entry and adverse event reporting. All faxed copies of source documents should be certified as outlined on page 9 of the DAIT Source Documentation SOP. The HIVTR Transplant Center

performing the transplant should keep an HIVTR source documentation binder on file with the original source documents that are faxed to the referring center. The subject would be transferred back to the referring center once the subject's acute post-transplant condition is stable.

Study monitoring will be done at the referring center performing the post-transplant follow-up.

## **10.6 SPECIMENS**

Refer to the Laboratory Manual for specimen collection, shipping, and tracking information. The most current Laboratory Manual can always be found on the study website at [www.emmes.com](http://www.emmes.com).

## 11 APPENDIX A: AACTG DEFINITION OF PANCREATITIS

---

Version 2.0, January 4, 2002

*Prepared by the Pancreatitis Subcommittee of the Complications of HIV Disease Research Agenda Committee*

### Background:

A formal definition of pancreatitis does not exist in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult Adverse Experiences. While there is no mention of asymptomatic or “chemical” pancreatitis, the laboratory values of amylase, pancreatic amylase, and lipase are given toxicity scoring values in the DAIDS document. The formal definition of pancreatitis has been left to the individual protocols; an example can be found in AACTG 384, section 6.571. This lack of an agreed upon definition has resulted in inconsistencies in reporting between protocols making cross-protocol analysis for prevalence and risks suboptimal.

### Current Definitions:

Pancreatitis will be reported as either clinical (i.e., symptomatic) or chemical (i.e., persistent elevation in enzymes without any symptoms). The principal enzyme abnormality that will be used for making diagnoses is the lipase level, as this is the most specific. If amylase determinations are made as part of standard of care, they will be recorded. Triglyceride values will be measured at the time of lipase determinations as is possible. Semi-quantitative assessments of clinical signs and symptoms associated with pancreatitis have been altered from previous DAIDS grading scales for nausea and vomiting to be more consistent and descriptive of the severity of pancreatitis (and to be used as such for scoring Toxicity Related Clinical Diagnoses). The preexisting DAIDS grading scales for nausea and vomiting, however, cannot be changed. Therefore, to avoid confusion, the assessment in pancreatitis cases will be described as severity levels, rather than grades.

### Nausea

Level 1: Mild or transient; reasonable intake maintained; lasting for <7 days.

Level 2: Moderate discomfort or intake decreased for  $\geq 7$  days.

Level 3: Severe discomfort or minimal intake for  $\geq 3$  days.

Level 4: Hospitalization required.

### Vomiting

Level 1: Mild or transient; 1-3 episodes per day or mild vomiting lasting <7 days.

Level 2: Moderate or persistent; 4-5 episodes per day or vomiting lasting  $\geq 7$  days.

Level 3: Severe vomiting of all food/fluids in 24 hours or orthostatic hypotension or intravenous treatment required.

Level 4: Hospitalization required.

### Abdominal Pain

Level 1: Mild. Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required; duration <7 days. No or minimal tenderness elicited on abdominal examination.

Level 2: Moderate. Mild to moderate limitation in activity; some assistance may be needed; no or minimal intervention/therapy required; or Grade 1 symptoms/signs lasting for  $\geq 7$  days. Tenderness on abdominal palpation is localized with minimal or no rebound.

Level 3: Severe. Marked limitation in activity; some assistance required; medical intervention/therapy required; marked local or diffuse tenderness with or without rebound present on abdominal examination.

Level 4: Life threatening. Extreme limitation in activity; significant medical intervention/therapy required; hospitalization required.

The clinical grading scales are designed to be consistent with each other in terms of the severity and chronicity of nausea, vomiting, or abdominal pain.

Toxicity grading designations for lipase have been made without regard to concomitant symptoms. They are based on the laboratory value as a proportion of the upper limits of normal (ULN) from the laboratory performing the assay. These values have been previously set in DAIDS toxicity tables and will not be adjusted.

A. Lipase:

Grade 1:  $>1.0 - 1.5 \times \text{ULN}$

Grade 2:  $>1.5 - 2.0 \times \text{ULN}$

Grade 3:  $>2.0 - 5.0 \times \text{ULN}$

Grade 4:  $>5.0 \times \text{ULN}$

Definition of Pancreatitis

1. For patients with any clinical symptoms raising the question of pancreatitis, especially abdominal pain:
  - a. Perform lipase (and triglyceride level). Record amylase if done as standard of care.
  - b. If lipase is Grade  $\geq 3$  and other diagnoses are reasonably excluded (e.g., renal insufficiency causing false elevations in lipase), diagnose clinical pancreatitis.
  - c. If lipase is Grade  $<3$ , patient will be observed with repeat testing within 2 weeks.
  - d. If lipase remains elevated but is still Grade  $<3$ , and symptoms persist, a CT scan will be ordered. CT findings of pancreatic enlargement and/or peripancreatic inflammation will indicate pancreatitis. (If a diagnostic radiology test other than CT was done during the workup that indicated the diagnosis of pancreatitis, that result will be accepted and a CT scan will not be required.) If the CT scan shows no evidence of pancreatitis, lipase will continue to be monitored every 2 weeks until symptoms and lipase abnormalities resolve.
  - e. If lipase is normal, search for other causes of symptoms. If none are found and symptoms persist, repeat lipase within 2 weeks.

2. For patients with no symptoms but with elevations in pancreatic enzymes:
  - a. Elevations of lipase of Grade  $\geq 3$  will trigger repeat testing within 2 weeks.
  - b. Persistence of asymptomatic elevation of lipase of Grade  $\geq 3$  will qualify as a diagnosis of chemical (asymptomatic) pancreatitis.
3. For both symptomatic and asymptomatic patients suspected of having pancreatitis, triglyceride levels should be drawn with lipase values.

#### Proposed Management of Drug Regimens in the Setting of Pancreatitis:

1. At the discretion of the study team (e.g., with asymptomatic lipase elevations), patients with a diagnosis of pancreatitis will have all medications stopped that are potentially causing pancreatitis.
2. If any of the drugs being held is an antiretroviral agent, all additional components of the antiretroviral regimen should be held.
3. The pancreatitis will be listed as an AE associated with the medication. The severity of clinical pancreatitis will be recorded by the highest severity level noted in any of the associated clinical signs and symptoms (level 4 will also be listed with severe). Asymptomatic, chemical pancreatitis will be listed as mild, regardless of enzyme elevation.
4. In a setting in which other concomitant illness might have reasonably contributed to the development of pancreatitis, and after the complete resolution of the episode, a decision to rechallenge the patient with the medication will be made by the protocol team. This will be done with biweekly lipase determinations for at least 6 weeks after the reinitiation of therapy. An elevation of lipase of Grade  $\geq 2$  or any recurrence of symptoms during this period will lead to permanent discontinuation of suspected medication with an AE grading of definite.

#### General Comments:

The clinical criteria for a diagnosis of pancreatitis in treatment studies usually require a threefold elevation in amylase or lipase and abdominal pain as the principal clinical symptom. The decision to require Grade 3 or more elevations ( $\geq$  twofold elevations in ULN) for the diagnosis of pancreatitis lowers the threshold for diagnosing pancreatitis as a toxicity associated with treatment protocols, and is a reasonable choice in the interest of patient safety. Greater specificity in diagnosis is achieved utilizing lipase measurements; therefore the definition of pancreatitis will rest on this value. Elevated triglycerides may be an important risk factor for pancreatitis and may be associated with the clinical event; therefore triglycerides are being measured with the lipase.

The principal symptom associated with the diagnosis of pancreatitis is abdominal pain. We have sought to align the various ratings of symptoms of nausea, vomiting, and abdominal pain in order to make them more consistent with each other. For safety purposes, any abdominal symptoms are accepted, but rating in this way may generate more useful information with regard to prodromal symptoms for analyzing the onset of pancreatitis.

The concept of reporting confirmed versus probable to describe the certainty with which a diagnosis is made is appropriate when there is a "gold standard" that is readily applied. This is not readily applied for the diagnosis of pancreatitis because biopsy or even

radiologic evidence is not achieved in many cases of clinical practice where there is a high comfort level with calling the diagnosis, and demanding a CT scan for clinically obvious diagnosis will be burdensome for the patient and protocols. Therefore, in reporting pancreatitis the case will be described as either clinical (symptomatic), or chemical (asymptomatic), with associated severity levels based on the signs or symptoms (in the case of clinical pancreatitis), or as mild (in chemical pancreatitis).

## 12 SAMPLE STANDING ORDER FOR HBIG

---

\*Note: Please refer to protocol for units of HBIG since dose varies.

1. \_\_\_\_\_ units HBIG IV over 2 – 4 hours
2. pre-medicate prior to infusion with:
  - a. acetaminophen 650 mg PO
  - b. diphenhydramine 25 – 20 mg PO
3. Infuse at 50 – 150 cc/hr depending on patient's tolerance
4. Call MD ( \_\_\_ - \_\_\_ for on call MD) for SOB, tachycardia > 110, myalgias, or back pain.
5. For back pain:
  - a. Meperidine 50mg IV/IM prn pain may repeat x 1.
6. For Questions, call \_\_\_\_\_ at \_\_\_\_\_.