**Policy: Pre and Post-Liver Transplant listing and management of the HIV-positive patient**

**Statement: Statement: Activation** **Date: 7/2013**
**Affected Department**: Liver transplant program
**Vision strategy**: Patient care
**Policy Statement**: The Emory Transplant Center will comply with all applicable federal, state and local laws, regulations and policies regarding the management of prescribing medications and refills.
**Basis**: This policy is necessary for the protection of patients, physicians and staff.
**Administrative Responsibility**: Section heads, physicians, practitioners, and staff are responsible for compliance with this policy.

**Scope/Procedure:**

**1. BACKGROUND**

Patients with HIV infection and end-stage liver disease (ESLD) were previously excluded from consideration for liver transplantation (LT) due to the short life expectancy from complications of acquired immune deficiency syndrome (AIDS). However, with the introduction of highly active anti-retroviral therapy (HAART), there was a rapid and significant decline in mortality from AIDS, from 29.4 per 100 person-years in 1995 to 8.8 per 100 person-years by 1997 (1). Similarly, the incidence of common opportunistic infections, such as *Pneumocystis jiroveci* pneumonitis, *Mycobacterium avium* complex diseases, and Cytomegalovirus retinitis, dropped from 21.9 to 3.7 per 100 person-years (*1*). Life expectancy for patients infected with HIV is now approaching that of the general population (*2*). Identification of concomitant HCV infection in patients with HIV is increasingly commonplace, which is not surprising given the similar risk factors for virus transmission (*3*

**2. Referral:**

Referrals will be received through the ETC Liver Transplant intake process using the standard program referral forms and requirements

Referral review by M.D.—pt identified as HIV positive and the diagnosis of HIV entered into the patient’s OTTR record

Patient will be scheduled to attend pre-transplant education class and sign letter of intent

Scheduling for day 1 evaluation

List created in OTTR to sort patients based on diagnosis of HIV to allow tracking

**2. Evaluation:**

Day 1 evaluation:

At day 1 evaluation, additional HIV labs will be ordered by MLP: HIV RNA and CD4 count

**Patient Education**

HIV positive patients will be educated by the mid-level provider or nurse coordinator regarding additional records required and medical criteria for transplantation for the HIV patient population. Patient will be provided with a copy of eligibility criteria “Patient Information” sheet outlining the medical criteria for HIV positive transplant. This document will be reviewed with the patient by the MLP and the patient will be asked to sign at the bottom acknowledging understanding of the information provided. A copy will be placed in the patient’s pre-transplant record. The patient will also be provided a copy of “Information for the Primary Care Provider” information sheet and encouraged to take this letter to his/her primary ID provider at the next visit. The patient will be instructed that ID records must be received before patient proceeds with evaluation. The records should be faxed to the pre-transplant coordinator by the patient’s primary medical care provider within 30 days.

**Records**

The MLP will have the patient sign a release of information for infectious disease records and obtain contact information for patient’s primary ID care provider. The patient will be made aware that at least one year historical records will be required prior to proceeding with evaluation. Records required will include:

one year history of lab results and office visit notes

anti-retroviral medication (**historical** and current)

opportunistic infection history

PPD result

The MLP will give the signed ROI to the medical secretary for faxing. The medical secretary will fax the ROI and the Information for the PCP letter, along with the fax coversheet for the patient’s pre-transplant coordinator. The patient’s ID provider information should be entered in OTTR in the Primary Care physician field by the medical secretary. These records should be scanned into EMR as soon as possible.

At conclusion of day 1 evaluation, the MLP will complete orders for medical testing and Day 2 lab testing and place in patient’s chart. Testing will not be scheduled until patient completes ID consult visit. Second eval visit with Liver Surgeon and with Transplant ID (Lyon, Mehta, Friedman) will be scheduled at least 30 days after day 1 eval.

If MLP determines patient is not a candidate for transplant on day one eval, after consultation with the surgeon, no further visits will be scheduled. The surgeon will dictate NAC letter to patient and referring MD. Referral will be closed.

**ID and Surgical consult visit**

Following day one evaluation, patients will be scheduled for ID consultation in Transplant ID clinic and surgical consultation. This appointment should be scheduled at least 30 days distant from day 1 visit on the physicians’ routine clinic schedule.

Historical ID records should be scanned into EMR prior to the Transplant ID appointment. If records have not been received, the patient may still have the ID and surgical consult appointments, however a determination about candidacy for continuing evaluation may be deferred until additional records are available.

If the patient is a “No Show” for this consult visit, s/he will be made NAC for evaluation. The Program director will dictate NAC letters to the patient and referring provider and they will be informed they will not be eligible for re-referral for 6 months. (reference: Correspondence Procedure)

The Transplant ID provider will make a determination regarding the patient’s candidacy relative to his/her HIV medical status, with the following eligibility criteria guidelines:

**INCLUSION CRITERIA**

To be eligible to proceed with evaluation, patients must have:

1. Documented HIV infection (by any licensed ELISA and confirmation by Western Blot).

2. Current CD4+ T-cell count >100/uL for > 6 months.

3. Nadir (lowest) CD4+ T-cell count >50/mm3\*.

4. HIV-1 RNA < 400 for >3 months\*. (Intermittent elevations to < 1000 copies/ml, if not persistent on more than two sequential measures and followed by undetectable levels, are permitted.) This criterion may be waived at the discretion of Transplant ID if the patient has been unable to tolerate ARV medications secondary to liver dysfunction and the patient meets all other eligibility criteria, including #7.

5. Be on antiretroviral therapy (exception, pt who has never been on ART and has undetectable VL, eligible CD4 count ie “Elite Controller”) and predicted to have l ongoing HIV suppression with the current ARV regimen

6. Willing to agree to start or re-start ARV therapy in the immediate post-operative period, and be willing to continue such therapy, or modify ARV therapy, at the direction of the clinician in conjunction with the primary care provider.

7. If the patient has HCV infection, must be willing to undergo frequent monitoring, including liver biopsies and treatment of HCV as recommended.

**EXCLUSION CRITERIA**

1. Any history of any AIDS-defining OI or neoplasm, except drug susceptible mucocutaneous candidasis or candida esophagitis.

2. History of active pulmonary or extrapulmonary tuberculosis; however latent TB is not an exclusion

3. History of pulmonary coccidiodomycosis will be treated per recommended treatment guidelines and generally should require a 5 year disease-free interval.

4. History of any neoplasm except for the following: cutaneous kaposi’s sarcoma, in situ anogenital carcinoma, adequately treated basal or squamous cell carcinoma of the skin, solid tumors (except primary CNS lymphoma) treated with curative therapy and disease free for more than 5 years. History of renal cell carcinoma requires disease-free state for 2 years. History of leukemia/lymphoma will be evaluated on an individual basis in consultation with Hematology/Oncology service

5. Inability or unwillingness to comply with immunosuppression protocol, ARV therapy, and/or HCV monitoring and therapy if indicated.

6. HIV genotype or phenotype demonstrating antiretroviral resistance in 3 drug classes (nucleoside reverse transcriptase inhibitors, non- nucleoside reverse transcriptase inhibitors, and protease inhibitors).

**3. UNOS Listing:**

Once evaluation process is completed and patient is found to be suitable candidate for transplant, Listing Packet will be sent to patient. Eligibility for transplant information sheet will be sent in the listing packet, reminding patients of the obligation to continue q 3 month follow-up with their ID provider and that updated CD4 count and HIV viral load laboratory test results must be forwarded to the transplant center every **100 days** in order for them to be considered for transplant when a donor organ is available. In this letter, the patient will be made aware that failure to submit required labs will result in them being made inactive (Status 7) on the UNOS waiting list.
“Information for Primary Care Provider: Patient Listing” information sheet will be mailed to the patients primary ID provider by the medical secretary at the time all other listing notifications are sent.

**4. Wait List Management:**

Status of Wait-listed patients will be reviewed every 3 months. While awaiting transplant, CD4 (number and percent), CD8 (number and percent), and quantitative HIV-1 viral load should be received by the Emory Transplant Center every 100 days. If updated HIV labs have not been submitted, a reminder call will be placed to the patient and the patient’s ID provider’s office. If required labs are not received within 30 days, the patient will be made status 7 on the UNOS wait list until such time as updated records are received. The HIV waitlist manager will notify the UNOS listing coordinator and the Program Director via OTTR email to change the patient’s status and a letter will be sent from Program Director informing the patient of status change.

No further patient follow-up or contacts will be initiated. Patient will remain Status 7 until updated records are received or until the patient is scheduled for re-evaluation per Program policy.

**5. Transplant:**

To be eligible for transplantation, at the time of the organ offer, patients must have**:**

HIV viral load of **<1,000** copies within the 16 weeks prior to the organ offer

CD4 count **>100/µL** within the 16 weeks prior to the organ offer

no active infections

be on antiretroviral therapy (exception, pt who has never been on ART and has undetectable VL, eligible CD4 count)

At the time of transplant, the team should sent a CD4 count and HIV viral load test. Transplant ID team should be consulted to start/restart appropriate antivirals and ensure the patient is still appropriate for transplantation.

**6. Post Transplant Management:**

A. At 4 week visit,

HIV Viral load

Transplant ID Clinic appointment

B. Every 3 months thereafter

HIV viral load

T cell subsets (CD4 count/percentage and CD8 count/percentage)

Follow up visit with HIV provider or Transplant ID

C. Transplant Infectious Diseases

The Transplant ID clinic will follow the patient following discharge, as needed, to assist with interactions between immunosuppression.

D. Immunosuppression

Patients will be maintained with standard immunosuppression protocol for Liver Transplantation, with the EXCEPTION that if the patient is on ritonavir containing regimen, the patient should receive only the first standard dose of tacrolimus. The dosing thereafter should be determined by discussion between the Transplant PharmD, the Liver Transplant Service and Transplant ID.

E. Antiretroviral Therapy

The FDA has approved five classes of antiretroviral agents. Highly active antiretroviral therapy (HAART), usually consists of three or more drugs from at least two different classes. Typically the antiretrovirals, on which the patient has been maintained, will be restarted.
\*\*Please note the significant interaction of ritonavir on metabolism of cyclosporine and tacrolimus.\*\*

**F. OPPORTUNISTIC INFECTION PROPHYLAXIS: RECOMMENDED REGIMENS**

**Pneumocystis Carinii Pneumonia (PCP)**

Indication: All HIV+ Liver transplant recipients

Regimen: Bactrim 1 single strength tablet PO daily **life-long**

Alternatives:

Dapsone 100 mg PO QDay (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 respirgard II nebulizer monthly.

**Toxoplasmosis**

Indication: Primary prophylaxis is indicated for Toxo IgG positive pts with CD4 count < 200. Secondary prophylaxis should be reinstituted immediately post-transplant for one month for any patient with prior history of Toxoplasmosis and whenever CD4 count drops below 200 cells. May be discontinued when CD4 count is >200 for 6 months.

Preferred Regimen: Bactrim SS 1 tab PO qday

Alternatives:

atovaquone 1500 mg PO Qday

dapsone 100 mg PO daily + pyrimethamine 50 mg PO QD + leucovorin 25 mg PO qday

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.)

**Mycobaterium Avium Complex (MAC)**

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

Indication: If CD4 count drops < 75 cells/µL. May be discontinued when CD4 count is above 100 cells/µL

Preferred Regimen: azithromycin 1200 mg PO weekly

Alternative:

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 Qday. Rifabutin must be administered at one-half the usual daily dose (i.e., reduce from 300 mg to 150 mg PO Qday) with protease inhibitors.

*Secondary Prophylaxis (Patients with a Prior History of DMAC)*

**Patients should be referred to Transplant ID for management**

Indication: if the CD4 count drops below 100 cells/µL. May be discontinued when CD4 count is above 100 for 6 months. Should also be reinstituted during treatment for AR and for one month following completion of AR therapy (unless CD4 count drops below 100)

**Cytomegalovirus (CMV)**

*Per Liver CMV protocol*

**Epstein Barr Virus (EBV)**

Patients who are EBV negative and receive a transplant from EBV positive donor will be monitored for EBV infection per standard of care.

**Cryptococcosis, extrapulmonary**

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

Regimen: None recommended

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

Preferred Regimen: fluconazole 200 mg PO QDay for 6 months.

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.

**Histoplasmosis**

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

Regimen: None recommended.

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

Preferred Regimen: itraconazole 200 mg PO BID taken with food x 6 months

Alternative: Recommendations will be made on individual basis after consultation with transplant ID provider.

**TB**

**Refer to TB protocol**

**Fungal prophylaxis**
Fluconazole or micafungin is given for antifungal prophylaxis following transplant procedures with elevated operative times or transfusion requirements from the first day post-LT to hospital discharge.
If no systemic antifungal prophylaxis is provided, nystatin suspension or clotrimazole troches should be given for the first 30 days after LT.

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