#. UWMC HIV+ Liver Transplant Recipients Clinical Management Guideline 1-14

Evaluation and Inclusion/Exclusion Criteria for Patient Selection:

General Criteria: As with non-HIV transplant candidates, the candidate must have an anticipated life expectancy of at least 5 years and otherwise conform to criteria for listing for non-HIV liver transplant recipients (See standard protocol for acceptance into UWMC liver transplant program). In addition the following must be true:

- Female patients of childbearing age must practice contraception and have a negative B-HCG pregnancy test.
- Willing to use PCP, herpes/CMV and fungal prophylaxis as indicated.

HIV Criteria: The patient must have well-established follow up with an ID HIV specialist. The patient must also undergo evaluation by the UWMC Transplant Infectious Diseases specialist*. Consultation with the UWMC Transplant ID specialist should occur as early as possible in the transplant evaluation process in order to consider optimal HAART regimens in light of potential future drug interactions. The specialist must find the patient strictly adherent with HAART therapy and to be on a stable regimen for at least 6 months. Other HIV treatment criteria that must be met include:

- HIV RNA levels undetectable for at least 6 months prior to transplant (Less than 40 copies/ml).
- At time of organ availability the most recent HIV RNA must be within 16 weeks prior to transplant.
- CD4 T-cell counts greater than or equal to 200/microliter for at least 6 months.
- HIV RNA and CD4 count shall be performed every 3 months.

OI Criteria: If there is a history of opportunistic infections (OIs), there should be no active disease after completing treatment for at least 1 year. The UWMC Transplant HIV consultant will make recommendations regarding the risks and advisability of immunosuppression in the setting of previous OI, as well as for secondary prophylaxis after transplantation. The patient must meet the following criteria for specific OIs:

- CMV retinitis: no active disease on ophthalmologic exam.
- Histoplasmosis, disseminated or extrapulmonary: must be on secondary prophylaxis.
- CNS toxoplasmosis: completed therapy and MRI without active disease.
- Cutaneous Kaposi's sarcoma: complete remission with immune reconstitution and no active/vascular residual cutaneous lesions on physical exam and neg chest CT scan.
- Cryptococcus: negative serum cryptococcal antigen.
- Mycobacterium avium intracellulare: No active disease. If prior disseminated disease, must have subsequent negative blood cultures.
- HIV-related encephalopathy:
  - Diagnosed prior to HAART
  - Resolved on HAART with marked improvement in mental status with increased CD4+ T-cell count
  - No evidence of progression of CNS disease
  - Otherwise considered eligible from a functional standpoint.

Other pre-transplant evaluations: Work up should follow the standard UWMC liver transplant guidelines. This includes serologic testing (HSV, CMV, VZV, EBV, syphilis, Hepatitis A, B, and C, measles, mumps, and rubella), evaluation for latent TB (IGRA – e.g. Quantiferon), consideration for testing based on other exposures (e.g. strongyloides, endemic fungi), and updated vaccinations (Tdap, Pneumovax/Prevnar, Influenza, Hepatitis A and B, VZV, and HPV, as appropriate). In addition, Hepatitis B and Hepatitis C nucleic acid testing should be performed, along with serologies for HHV-8, HTLV1, and toxoplasma.

***UWMC Transplant HIV consultants:** Robert Rakita, MD, Cynthia Fisher, MD, Erika Lease, MD, Ajit Limaye, MD, John Scott, MD, Geoffrey Gottlieb, MD
UWMC HIV pharmacist: Rupali Jain, Pharm. D.

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Exclusion criteria: The following are generally considered relative contraindications to liver transplant for HIV+ recipients, but should be evaluated on a case by case basis:

- BMI<21
- Significant renal dysfunction (CrCl <50 ml/min)
- History of life-threatening reactions to sulfa, such as Stevens Johnson Syndrome.
- HCV positive donor
- Demonstrated ongoing non-compliance with medical treatment.
- Documented history of progressive multifocal leukoencephalopathy, extracutaneous Kaposi's sarcoma, EBV and HHV8 related lymphoproliferative disorders, or primary CNS lymphoma.
- History of other neoplasia except for: cutaneous Kaposi's sarcoma as outlined above, in situ anogenital carcinoma, treated basal or squamous cell carcinoma of the skin, solid tumors and leukemia treated with curative therapy and disease free for duration as outlined in UWMC standard transplant inclusion criteria (≥2 - 5 year disease free depending on type of primary tumor).
- Concurrent chronic infection with HTLV-1.
- Significant cardiovascular or pulmonary disease, or psychosocial issues that may exclude a patient are as outlined in standard UWMC transplant acceptance criteria.

Interaction management:
There are significant interactions between the drugs used to treat HIV (HAART) and immunosuppressive drugs, in particular calcineurin inhibitors and mTOR inhibitors. Other transplant pharmacotherapy can also interact with HAART (i.e. ranitidine/PPI's and atazanavir). Check with the clinical pharmacist to discuss medication interaction issues. Monitoring of immunosuppressive drug levels is essential to managing these interactions.

- Drug levels shall be obtained daily during inpatient stay until stabilization, then 2-3 times per week.
- More intensive monitoring may be required, particularly if HAART regimen is modified later in life after transplant (HAART regimen should not be changed peri-transplant)
- See target trough blood levels of standard protocol.

Drugs used for HAART include: protease inhibitors (PIs), nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase inhibitors, fusion inhibitors, and CCR5 antagonists.

The basic treatment structure for HAART is: 2 NRTI + boosted PI or NNRTI or integrase inhibitor. Alternate treatment structure may be used with more advanced patients. It is essential the patient continues on their home HAART regimen peri-transplant without interruption. The HAART regimen should not be changed in the peri-transplant period. In the case of life-threatening toxicity, discuss any deviation from HAART therapy with the UWMC Transplant HIV consultants. See HIV+ Liver HAART Therapy Appendix for the list of individual drugs and drug interaction issues (see also *Transplantation Proceedings,* 41, 3796–3799 (2009)**,** and http://www.aidsinfo.nih.gov/guidelines/, go to Adult and Adolescent Guidelines).

Treatment of Rejection:
Treated rejection should always be documented by biopsy if possible. Acute rejection should be treated with pulse steroid protocol according to the standard guideline for Liver Rejection. Use of anti-thymocyte globulin may be considered for treatment of severe rejection or as rescue therapy after careful discussion with the patient weighing the risks of infection and malignancy versus risk of graft loss. See standard protocol for steroid pulse doses and prednisone tapers.

References

1. Terrault NA, Roland ME, Schiano T, et al. Outcomes of liver transplant recipients with hepatitis C and human immunodeficiency virus coinfection. Liver Transplantation 2012; 18:716-726.
2. Coffin CS, Stock, PG, Dove LM, et al. Virologic and clinical outcomes of hepatitis B virus infection in HIV-HBV coinfected transplant recipients. Am J Transplant 2010; 10:1268-1275.

#. HIV+ Liver Recipient Induction Immunosuppression Guideline 1-14

Induction: Steroid only induction will be used, with the dosing schedule as follows:

Day Post-OP	Steroid	Day Post-OP	Steroid
0	Methylpred 1gm IV x1 (OR)	6	Prednisone 30mg po QDay
1	Methylpred 500mg IV x1	7-9	Prednisone 25mg po QDay
2	Methylpred 400mg IV x1	10-16	Prednisone 20mg po QDay
3	Methylpred 300mg IV x1	17-23	Prednisone 15mg po QDay
4	Methylpred 200mg IV x1	24-30	Prednisone 12.5 mg po QDay
5	Methylpred 100mg IV x1	≥31	Prednisone 10mg po QDay

Maintenance immunosuppression: Two-drug maintenance immunosuppression will be used initially for all patients. **Tacrolimus (Prograf®)** will be started on POD 0 or 1. The appropriate tacrolimus dosing regimen shall be determined in consultation with the attending surgeon, Transplant ID and the Transplant Clinical Pharmacist in anticipation of clinically significant drug-drug interactions between HAART and CNI (See Appendix). Cyclosporine modified shall be reserved as a second-line calcineurin inhibitor used when the patient has intolerance or allergy to tacrolimus.

Tacrolimus Dosing:

- PI-containing regimen, or patients on Stribild® (Elvitegravir/cobicistat/emtricitabine/tenofovir): Give a "mini" loading dose 1-2mg PO x 1. Then check the tacrolimus blood level QAM and re-dose with 0.5mg PO x1 when level < 10ng/ml (or as directed by attending), typically in 3-5 days. Maintenance dosing is typically 1 to 2 times **per week**.
- Non-PI regimens: 0.025mg/kg (rounded to nearest 0.5mg) PO q12h, adjust dose normally.
- Tacrolimus level goal for all patients is 8-10 ng/ml for months 0-3.

Cyclosporine Dosing (2nd line if unable to tolerate tacrolimus)**:**

- PI-containing regimen or patients on Stribild® (Elvitegravir/cobcistat/emtricitabine/tenofovir): Cyclosporine modified 25mg PO q12h, adjust dose normally.
- NNRTI-containing regimen without PI: 5mg/kg (rounded to the nearest 25mg) PO q12h, adjust dose normally.
- Non-PI, non-NNRTI regimen: no change from standard.
- Check with attending for goal cyclosporine level and monitoring strategy (C0 vs. C2 vs. C4).

Corticosteroid Dosing: After day 31, a further taper to lower maintenance doses or off can be considered. If the patient was taking prednisone prior to transplant or prednisone is being added after receiving induction, resume maintenance dose; no taper required. Note interaction between PI-containing regimen or Stribild and corticosteroids, with increase in steroid effect.

Sirolimus Dosing: (for high risk HCC patients)

- PI-containing regimen, or patients on Stribild® (Elvitegravir/cobicistat/emtricitabine/tenofovir): Use with caution and extended dosing intervals. 1mg PO x1 then follow levels and re-dose when trough within target range. Typical dosing is 1mg every 3-5 days (or 1.5mg weekly)
- NNRTI-containing regimen without PI: Usual dosing, may require higher doses to maintain trough
- Non-PI, non-NNRTI regimen: no change from standard.
- Sirolimus level goal for all patients is 5-8 ng/ml for the first 3 months, ~5 ng/ml thereafter.

Mycophenolate mofetil (MMF) Dosing:

- **Mycophenolate mofetil (Cellcept®)** shall only be used as an alternative.
- Drug level monitoring (MPA level) is generally not performed unless toxicity is suspected.

#. HIV+ Liver Recipient Induction Guideline

Day Post-Op	Steroid Taper	Tacrolimus (Prograf®, FK506)
Intra-op **Day 0**	Methylprednisolone 1000mg IV	PI containing HAART regimen: 1-2mg PO x 1 if not given pre-op Non-PI HAART regimen: start at 0800 or 2000 after returning to floor 0.025mg/kg po bid (round to nearest 0.5mg)
Day 1	MP 500mg IV	Monitor daily tacrolimus level, adjust for goal level: 8-10 ng/ml PI containing HAART regimen: single dose of 0.5-1mg when level <10 Non-PI HAART regimen: Adjust dose similar to non-HIV patient
Day 2	MP 400mg IV	same
Day 3	MP 300mg IV	same
Day 4	MP 200mg IV	same
Day 5	MP 100mg IV	same
Day 6	Prednisone 30mg po QDay	same
Day 7-9	Prednisone 25mg po QDay	same
Day 10-16	Prednisone 20mg po QDay	same
Day 17-23	Prednisone 15mg po QDay	same
Day 24-30	Prednisone 12.5 mg po QDay	same
Day 31+	Prednisone 10mg po QDay, *consider further taper if indicated*	same

#. HIV+ Liver Recipient Infection Prophylaxis Guideline 1-14

Primary Prophylaxis (no history of infection): Patients will receive standard antimicrobial prophylaxis for prevention of surgical infection, non-invasive candida, and primary prophylaxis of CMV or HSV similar to non-HIV+ Liver recipients. Patients may require additional primary prophylaxis for other infections based on CD4 count or other recipient/donor risk factors (see table below).

Secondary Prophylaxis (patient with history of opportunistic infection): Patients with a history of the following OIs may require additional, prolonged or different prophylaxis after transplant (see table below).

	Primary Prophylaxis	Secondary Prophylaxis
CMV	**D(+)R(-):** Ganciclovir 5mg/kg IV q24h while NPO, then Valganciclovir 900mg po qd (3 mo) **R(+):** pre-emptive therapy (see guideline) (3 mo) **D(-)R(-):** Acyclovir 5mg/kg IV q8h while NPO then 400mg po bid (1 mo)	**Prolong normal prophylaxis if CD4 ≤ 100 DC when CD4 > 200 x 6 mo.** Valganciclovir 900mg po qday (dose adjusted for renal impairment)
HSV	**See standard protocol.**	*Consult transplant ID if history of recurrent or severe outbreak*
Pneumocystis pneumonia	**LIFELONG for all patients** Trim/Sulfa 80/400mg(ss) po qhs OR Dapsone 100mg po qday (check G6PD) OR Pentamidine 300mg inhaled qmonth *For sulfa allergy consider desensitization to sulfa to enable use of Trim/Sulfa.* *Note that dapsone or pentamidine are not adequate alone for Toxoplasma prophylaxis.*	Same as primary prophylaxis
Toxoplasma gondii	**If D (+)or R(+) LIFELONG** Bactrim DS 1 tab po qhs OR SS qhs OR Bactrim SS qhs OR Dapsone 50mg po qday + Pyrimethamine 50mg po qweek + Leucovorin 25mg po qweek OR Atovaquone 1500mg po daily	**Lifelong as secondary prophylaxis** Pyrimethamine 25-50mg po qday + Sulfadiazine 500-1000mg po qid + Leucovorin 25mg po qday *(covers PCP as well so can d/c PCP px)* OR Pyrimethamine 25mg po qday + Clindamycin 600mg po qid + Leucovorin 25mg po qday *(does NOT cover PCP)*
Mycobacterium Avium Complex (MAC)	**If CD4 ≤ 50. DC when CD4 >100 x 6 mo.** Azithromycin 1200mg po qweek OR Clarithromycin 500mg po bid *(CYP 3A4 inhibitor can ↑ CNI levels)*	**Indication: post-tx or rejection treatment or if CD4≤ 50. DC when CD4 >100 x 6 mo.** Azithromycin 600mg po qday + Ethambutol 15mg/kg/day OR Clarithromycin 500mg po bid + Ethambutol 15mg/kg/day
Cryptococcus	**None**	**Indication: post-tx or rejection treatment or if CD4≤200. DC when CD4>200 x 6 mo.** Fluconazole 200mg po qday
Histoplasmosis	**While CD4 count <150 and at high risk due to residing in endemic area.** Itraconazole 200mg po qday with food *Consider monitoring itraconazole levels.* *Oral solution has improved bioavailability(taken without food)* OR Fluconazole 400mg po qday	**Indication: post-tx or rejection treatment or if CD4≤150. DC when CD4>150 x 6 mo.** Itraconazole 200mg po qday with food *Consider monitoring itraconazole levels.* *Oral solution has improved bioavailability(taken without food)* OR Fluconazole 400mg po qday
Coccidioides	**Lifelong if IgG+ or IgM+ and from high risk area.** **Lifelong if donor hx of coccidioides.** Fluconazole 400mg po qday OR Itraconazole 200mg po bid	**Lifelong as secondary prophylaxis** Fluconazole 400mg po qday. OR Itraconazole 200mg po bid