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Journal

Liver Transplantation, 19(6)

ISSN

1527-6465

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Publication Date

2013-06-01

DOI

10.1002/lt.23648

Peer reviewed

Published in final edited form as:
Liver Transpl. 2013 June ; 19(6): 619–626. doi:10.1002/lt.23648.

Chronic Kidney Disease (CKD) after Liver Transplantation in HIV/HCV Coinfected versus HIV/non-HCV Infected Recipients: Results from the NIH Multi-Site Study

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Abstract

Hepatitis C virus (HCV) and Human Immunodeficiency Virus (HIV) are both associated with chronic kidney disease (CKD), a major complication after orthotopic liver transplantation (OLT). The aim of this study was to assess predictors of post-OLT CKD in HIV/HCV coinfected versus HIV/non-HCV infected recipients.

METHODS—Data from the NIH Solid Organ Transplantation in HIV: Multi-Site Study of 116 OLT recipients (35 HIV/non-HCV and 81 HIV/HCV co-infected) from 2003 to 2010 were analyzed for pre-transplant CKD prevalence (estimated glomerular filtration rate (eGFR) < 60 ml/min for ≥ 3 months) and incidence of CKD up to 3 years post-transplant. Proportional hazards models were performed to assess predictors of post-transplant CKD. A contemporaneous cohort of HCV monoinfected transplant recipients from the SRTR database was also analyzed.

RESULTS—Median age at transplant was 48 years, serum creatinine was 1.1 mg/dl, and median eGFR was 77 ml/min. Thirty-four patients had suspected pre-transplant CKD; 20 of these (59%) had post-transplant CKD. Among the 82 patients without pre-transplant CKD (26 HIV/non-HCV and 56 HIV/HCV coinfected), the cumulative incidence of stage 3 CKD at 3 years post-OLT was 62% (55% HIV/non-HCV versus 65% HIV/HCV coinfected) and stage 4/5 CKD was 8% (0% HIV/non-HCV versus 12% HIV/HCV coinfected). In multivariate proportional hazards analysis, older age (HR 1.05 per year; p 0.03) and CD4 count (HR 0.90 per 50 cells/μL; p 0.01) were significant predictors of CKD. HCV coinfection was significantly associated with stage 4/5 CKD (HR 10.8; p 0.03) after adjustment for age on multivariate analysis. The cumulative incidence of stage 4/5 CKD was significantly higher in HIV/HCV coinfected patients compared to HIV/non-HCV and HCV monoinfected transplant recipients (p=0.001).

CONCLUSIONS—CKD occurs frequently in HIV infected transplant recipients. Predictors of post-transplant CKD include older age, and lower post-transplant CD4 count. HCV co-infection is associated with a higher incidence of stage 4/5 CKD.

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BACKGROUND

Chronic Kidney Disease (CKD), defined by the National Kidney Foundation as the presence of a reduced glomerular filtration rate (GFR) for 3 months or longer, is a common complication after orthotopic liver transplantation (OLT) and has a major impact on graft and patient survival.[1–2] The presence of CKD post-transplant is not only important with respect to the need for renal replacement therapy, but also increases the risk for cardiovascular disease and mortality, emphasizing the need for protection of renal function after liver transplantation.[3] Hepatitis C virus (HCV) infection has been shown to be a risk factor for chronic kidney disease in liver transplant recipients due to an increased incidence of glomerular disease, as well as the association between HCV and diabetes, an established CKD risk factor.[4–6]

It is estimated that approximately 25–30% of patients with human immunodeficiency virus (HIV) are coinfected with HCV.[7] Individuals coinfected with both viruses are at risk for accelerated liver disease and consequently cirrhosis, liver failure, and hepatocellular carcinoma.[8] HIV infection has also been associated with a spectrum of kidney diseases including HIV associated nephropathy (a major cause of nephrotic syndrome in HIV infected patients), immune complex glomerulonephritis, thrombotic microangiopathy, and nephrotoxicity from antiretroviral therapy such as the nucleotide reverse transcriptase inhibitor tenofovir (proximal tubular dysfunction) and the protease inhibitor indinavir (nephrolithiasis, obstructive nephropathy, and interstitial nephritis).[9–10]

As an increasing number of patients coinfected with HIV and HCV are undergoing liver transplantation, the impact of HIV/HCV coinfection on post-transplant chronic kidney disease is an important outcome to study, particularly in the setting of calcineurin inhibitor immunosuppression. The aim of this study was to evaluate the incidence of post-transplant chronic kidney disease in HIV/HCV coinfected liver transplant recipients with the hypothesis that these patients have worse post-transplant kidney function than HIV/non-HCV infected transplant recipients.

METHODS/STATISTICAL ANALYSIS

Data obtained from a prospective multicenter study (NIH Solid Organ Transplantation in HIV: Multi-Site Study) of 125 HIV infected orthotopic liver transplant recipients between 2003 and 2010 were analyzed in order to assess the pre-transplant prevalence of CKD (estimated glomerular filtration rate (eGFR) < 60 ml/min for ≥ 3 months) and the incidence of CKD at 1 and 3 years post-transplant. There were 9 simultaneous liver/kidney transplant recipients in the database and these patients were excluded from our analysis. The remaining 116 patients were divided into two cohorts: those with HIV/HCV coinfection and those without HCV (Figure 1). Eighty-one patients in the cohort were HIV/HCV co-infected and 35 patients were not infected with HCV (23 of these were Hepatitis B virus infected). While data on matched HCV mono-infected patients were collected in the prospective database, only pre-transplant kidney function was available and hence post-transplant renal outcomes could not be assessed in this cohort as a comparison group. Data from the Scientific Registry of Transplant Recipients (SRTR) were analyzed to assess the prevalence of pre-transplant CKD and the incidence of CKD after transplantation in all orthotopic liver transplant alone recipients with a positive HCV serology during a similar time frame.

The primary outcome assessed was the incidence of chronic kidney disease at 1 and 3 years post-transplantation, with the focus being on the comparison between HIV/HCV coinfected patients and HIV positive patients without concomitant HCV. The eGFR was determined using the 4-point Modification of Diet in Renal Disease (MDRD) equation that is based on

serum creatinine, age, sex, and race.[11] Baseline and quarterly eGFR levels through year 3 post-transplant were used in the analysis.

Variables analyzed in our study included age (donor and recipient), race, gender, HIV viral load and CD4 count (both pre and post-transplant), eGFR at transplant, HAART (highly active anti-retroviral therapy) regimen (defined as time varying covariates of tenofovir, D4T/DDI or any protease inhibitor use within the prior 3 months), presence of diabetes (pre-transplant as well as *de novo* post-transplant, inferred in the database by the use of insulin or oral hypoglycemic therapy), hypertension (defined by the use of anti-hypertensives), most recent Model for End-Stage Liver Disease (MELD) score pre-transplant, incidence of acute cellular rejection, cytomegalovirus (CMV) infection, HCV therapy (post-transplant), the presence of proteinuria post-transplant, Hepatitis B virus (HBV) status, serum albumin, initial immunosuppression regimen (tacrolimus versus cyclosporine), and cyclosporine use in prior 3 months (as a time-varying covariate).

Statistical analyses were performed with SAS software, version 9.2 (SAS Institute, Cary, NC). A two-sided p value of less than 0.05 was considered to indicate statistical significance. Descriptive statistics included percentage, median, and interquartile range (IQR) as appropriate. Comparison of baseline characteristics was conducted using the Fisher's exact test (categorical variables) or Wilcoxon rank-sum test (continuous variables).

Kaplan-Meier analysis was performed for the time to development of chronic kidney disease after transplant in patients without pre-transplant renal dysfunction. Patients were censored at last follow-up. Estimated rates of CKD were calculated with the Kaplan–Meier method, and 95% confidence intervals were estimated with the Greenwood's formula. Survival distributions were compared by the log-rank test. In subjects without pre-transplant CKD, proportional hazards models were performed to assess for predictors of post-transplant CKD and stage 4/5 CKD. All variables with $p < 0.1$ from the univariate model were included in an initial multivariate model. Subsequently, variables with $p \geq 0.1$ were excluded, the model was re-fit, and all interactions examined. The impact of post-transplant CKD (as a time varying covariate) on graft loss and death was also evaluated in our cohort via univariate proportional hazards models.

RESULTS

Seventy-eight percent of the 116 study patients were male, 69% were Caucasian, and the median age at transplant was 48 years [interquartile range (IQR) 43–52]. The median pre-transplant serum creatinine level was 1.1 mg/dl [IQR 0.8–4.4] and eGFR was 77 ml/min [IQR 56–111]. The median post-transplant follow-up in the study was 3.6 years [IQR 2.2–5.0].

Thirty four of the one-hundred sixteen patients in the study cohort (29%) had suspected pre-transplant CKD with an eGFR < 60 ml/min; 25 of these patients were HIV/HCV coinfected and 9 were HIV/non-HCV. Twenty-two patients had an eGFR between 30 and 60 ml/min (stage 3 CKD), 9 patients between 15 and 30 ml/min (stage 4 CKD) and 3 patients between 10 and 15 ml/min (stage 5 CKD) prior to transplantation. Among these 34 patients, 20 (59%) had at least stage 3 CKD post-transplant (6 had stage 4/5 CKD). In the cohort assessed using SRTR data, of the 11,436 liver transplant recipients identified with a positive HCV serology, 33% had suspected pre-transplant CKD (22% had stage 3 CKD, 8% had stage 4 CKD, and 3% stage 5 CKD).

Of the 82 patients without pre-transplant chronic kidney disease, 26 were HIV/non-HCV and 56 were HIV/HCV coinfected. The median age in this cohort was 48 years [IQR 43–52]. Among the 6594 HCV/non-HIV SRTR patients without pre-transplant chronic kidney

disease, the median age at transplant was 54 years [IQR 50–57], which was significantly higher than that for the HIV cohort (p<0.0001). The median MELD score at transplant was significantly lower in HCV/non-HIV group (15) compared to HIV/HCV coinfected group (18) and HIV/non-HCV group (16) (p=0.005). There was no difference among the applicable groups with respect to pre-transplant characteristics including eGFR at transplant (p=0.59), presence of pre-OLT diabetes (p=0.64), gender (p=0.54), or race (p=0.24) (Table 1). Eighty eight percent of HIV/HCV coinfected patients had an undetectable HIV RNA at enrollment compared to 85% in the HIV mono-infected group (p=0.74). Median donor age was 43 years in the HIV/HCV coinfected and HCV mono-infected groups versus 42 years in the HIV mono-infected group (p=0.80).

Post-transplant characteristics including the incidence of acute cellular rejection (p=0.63), CMV infection (p=0.30), diabetes (p=0.34) and hypertension (p=0.31) were also not significantly different between the HIV/HCV coinfected and HIV/non-HCV groups (Table 1).

Forty one of the 82 patients without pre-transplant CKD (50%) experienced chronic kidney disease post-transplant; 11 of those patients went on to develop stage 4/5 CKD (5 within 3 years, and 6 between 3 and 5 years post-transplant). Information on requirement of renal replacement therapy was not systematically collected in the database in order to determine the incidence of end-stage renal disease. The overall cumulative incidence (95% confidence interval) of stage 3 and stage 4/5 CKD in HIV cohort was 30% (21–43%) and 1% (0–9%) at 1 year post-transplant, respectively. At 3 years post-transplant, the corresponding cumulative incidence of stage 3 CKD was 62% (55% in HIV/non-HCV infected patients versus 65% in HIV/HCV coinfected patients) and stage 4/5 CKD was 8% (0% in HIV/non-HCV infected patients versus 12% in HIV/HCV coinfected patients) (Table 2). Among the 15 HIV/HBV coinfected patients without pre-transplant CKD in our cohort, 8 developed stage 3 CKD post-transplant and no patients developed stage 4/5 CKD. In SRTR HCV/non-HIV subjects without pre-transplant CKD, the cumulative incidence (95% confidence interval) of stage 3 and stage 4/5 CKD was 23% and 2.2% at 1 year post-transplant respectively. At 3 years post-transplant, the corresponding cumulative incidence of stage 3 and stage 4/5 CKD was 32% and 6.1%. Time to development of CKD and stage 4/5 CKD are shown in the Kaplan-Meier plots (Figures 2 and 3). The cumulative incidence of CKD was significantly lower in HCV/non-HIV controls compared to HIV/HCV coinfected or HIV/non-HCV subjects (log-rank test; p< 0.0001). On the other hand, cumulative incidence of stage 4/5 CKD was significantly higher in HIV/HCV coinfected subjects compared to both HIV/non-HCV and HCV/non-HIV subjects (log-rank test; p=0.001).

In the multivariate proportional hazards model, higher CD4 count (as a time-varying covariate) post-transplant was associated with a significantly lower risk of CKD (HR=0.90 per 50 cells/μL; p=0.01) and older age was associated with a greater incidence of CKD (HR=1.05 per year; p=0.03). Higher baseline eGFR was marginally associated with a lower incidence of CKD (HR=0.99 per ml/min; p=0.08). Cyclosporine use in prior 3 months, another significant predictor in the univariate model (HR=1.87; p=0.048), lost its significance in the multivariate model. HBV coinfection, HCV coinfection, race, diabetes, hypertension, the presence of proteinuria, and HAART regimen had no significant impact on development of CKD post-transplant (Table 3).

There were only 11 cases of stage 4/5 CKD post-transplant in our study. In the univariate proportional hazards regression models, HCV co-infection (HR=9.7; 95% CI 1.2–77.8; p=0.03), age (HR=1.09, 95%CI: 1.01–1.18; p=0.02) and female gender (HR=3.9, 95%CI: 1.2–13.1; p=0.03) were the only factors significantly associated with stage 4/5 CKD. In the multivariate model, HCV co-infection (HR=10.8, 95%CI: 1.3–89.4; p=0.03) and age

(HR=1.12, 95%CI: 1.01–1.25; p=0.03) remained statistically significant (while female gender was excluded (p=0.09)) (Table 4).

In univariate proportional hazards models, post-transplant CKD was not significantly associated with increased risk of death (HR=1.24; 95% CI: 0.51–3.00; p=0.64) or graft loss (HR=0.87; 95% CI: 0.37–2.02; p=0.74) after transplantation.

DISCUSSION

Administration of effective antiretroviral therapy has changed the natural course of human immunodeficiency virus (HIV), leading to a dramatic improvement in patient survival.[12] As a consequence, liver disease is now the leading cause of mortality among HIV-positive individuals, particularly those coinfected with chronic Hepatitis C virus (HCV), and HIV is no longer considered a contraindication to orthotopic liver transplantation.[13–14] Chronic kidney disease is a major contributor to post-liver transplant morbidity and mortality, and both HIV and Hepatitis C have been associated with kidney disease of several origins. There have been limited data thus far on renal outcomes after liver transplantation in patients coinfected with HIV and HCV.

The results from our study reveal that CKD is prevalent both pre and post-transplant in HIV positive liver transplant recipients. Among 116 patients evaluated in the study, 29% (34 patients) had pre-transplant chronic kidney disease and 12 patients (approximately 10% of the cohort) had stage 4/5 chronic kidney disease prior to transplant. Despite national guidelines that suggest consideration of simultaneous liver-kidney transplantation in patients with stage 4 CKD, these patients received liver transplantation alone.[15] Importantly, only 59% of the patients with suspected pre-transplant CKD had an eGFR < 60 ml/min post-transplant. Six patients (18% of the cohort with pre-transplant CKD) had stage 4/5 CKD after transplantation. Given that pre-transplant renal dysfunction is the most important determinant of post-transplant CKD,[16] the low rates of post-transplant CKD in this subset of patients are reassuring. This may potentially reflect the emphasis on renal sparing immunosuppression strategies in this patient cohort; however, these optimistic results could also be due to the limited median post-transplant follow-up of 3.6 years.

Among patients without baseline CKD prior to transplant, 62% developed stage 3 CKD and 8% developed stage 4/5 CKD at three years post-transplant. In univariate analysis, pre-transplant eGFR, a known predictor of post-transplant renal function, was significantly associated with post-transplant CKD. However, in the multivariate analysis, eGFR was marginally predictive of post-transplant CKD.

Despite our hypothesis, HCV co-infection was not a significant predictor of post-transplant CKD in HIV positive liver transplant recipients in our study in univariate or multivariate analyses. The lack of association between HCV and post-transplant CKD may be attributable to the similar incidence of diabetes in the HIV/HCV coinfected versus HIV/non-HCV cohorts in our study. Diabetes has been cited as a potential mechanism for worse renal outcomes in HCV liver transplant recipients.[17] Furthermore, recent data have revealed no worse post-transplant renal outcomes in patients with HCV cirrhosis and normal pre-liver transplant renal function compared to those with other causes of liver disease.[18] Analysis of liver transplant recipients with a positive HCV serology during a similar time frame using SRTR data also revealed a lower cumulative incidence of stage 3 (32%) and stage 4/5 (6.1%) CKD at 3 years post-transplant compared to the HIV/HCV coinfected cohort whose cumulative incidence of stage 3 and stage 4/5 CKD was 65% and 12% respectively.

Although there was no association between HCV and post-transplant CKD in our study, all patients with normal pre-transplant renal function who developed at least stage 4 CKD post-

transplant were HIV/HCV coinfected. Furthermore, the cumulative incidence of stage 4/5 CKD was significantly higher in the HIV/HCV coinfected compared to the HIV/non-HCV cohort at 12% versus 0% respectively (Figure 3). The event numbers were small for a robust analysis, but this raises the possibility of an association that could be confirmed with a larger sample size and/or longer duration of follow-up as our multivariate analysis did suggest an association between HCV co-infection and stage 4/5 post-transplant CKD (HR 10.8, p=0.03). Our results suggest a possible synergistic effect of HIV and HCV coinfection on the development of advanced post-transplant renal disease given the higher incidence of stage 4/5 CKD in these patients compared to HIV/non-HCV and HCV monoinfected controls respectively.

Older age and lower CD4 counts were significant predictors of post-transplant CKD in our study in multivariate analysis. Increasing age is a well-known predictor of post-transplant CKD, with a relative risk per 10-year increment of 1.36, based on observations by Ojo et al. in a population based cohort study assessing the risk factors for and incidence of CKD in non-renal transplant recipients.[19] In our study, there was a 5% increase in risk of CKD for every year increment in recipient age (p=0.03). Higher CD4 counts were protective against post-transplant CKD in our study. Perhaps this was due to a reduced incidence of HIV nephropathy post-transplant, a common cause of CKD in HIV infected individuals associated with a low CD4 count.[20] unfortunately, we do not have comprehensive data on post-transplant proteinuria or histological data from renal biopsies to assess the incidence of HIV associated focal segmental glomerulosclerosis in this cohort.

HAART therapy was not associated with post-transplant CKD in our analysis. Given the significant drug interactions between antiretroviral therapy and calcineurin-inhibitor based immunosuppression, it is possible that vigilant monitoring of renal function in these patients resulted in fewer cases of post-transplant CKD, and therefore no association was found between HAART and renal dysfunction in univariate and multivariate analyses. Cyclosporine use in prior 3 months, which was a significant predictor in the univariate model (HR=1.87; p=0.048), lost its significance in the multivariate model for CKD. The impact of immunosuppression trough levels were also assessed, but no association with post-transplant CKD was observed.

We also assessed the impact of post-transplant CKD on graft loss and death and found no significant association between post-transplant renal dysfunction and graft loss (p=0.74) or mortality (p=0.64). This is likely due to the small percentage of patients with significant post-transplant CKD and the relatively abbreviated follow-up in our study. A recent publication from the NIH sponsored Organ Transplantation in HIV study (HIV-TR) revealed 3 year patient and graft survival rates of 60% and 53% respectively in HIV/HCV coinfected patients.[21]

The strength of our study lies in its large sample size. The NIH HIV Solid Organ Transplant Multi-Site Study represents the largest cohort of HIV positive transplant recipients from 21 centers in the U.S. Limitations include median follow-up of approximately 3.5 years post-transplant, making it difficult to assess longer term renal outcomes after liver transplantation. Additionally, we did not have thorough data on pre and post-transplant proteinuria in our patients, an important variable in the assessment of kidney disease. Furthermore, histological data regarding etiology of post-transplant kidney disease were not assessed in our study in order to determine the mechanism for post-transplant CKD in our cohort. Another limitation of our analysis was the lack of HCV RNA status in the SRTR HCV mono-infected control group, so it is possible that some of the controls did not have HCV viremia at the time of transplant. Nonetheless, our data reveal that CKD is prevalent both prior to, and after liver transplantation in HIV/HCV coinfected patients, and the

incidence of advanced chronic kidney disease is 12% (95% CI: 5–28%) at 3 years post-transplant in this patient cohort. Important predictors of CKD include increasing age and lower CD4 counts after transplantation. Hepatitis C coinfection may be associated with a higher incidence and burden of advanced chronic kidney disease in the long term.

Acknowledgments

The authors thank all of the Solid Organ Transplantation in HIV: Multi-Site Study investigators and coordinators for their hard work and dedication to the study and subjects.

GRANT SUPPORT

"Supported by the Solid Organ Transplantation in HIV: Multi-Site Study (AI052748) funded by the National Institute of Allergy and infectious Diseases (ClinicalTrials.gov number, NCT00074386.) The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy And Infectious Diseases or the National Institutes of Health."

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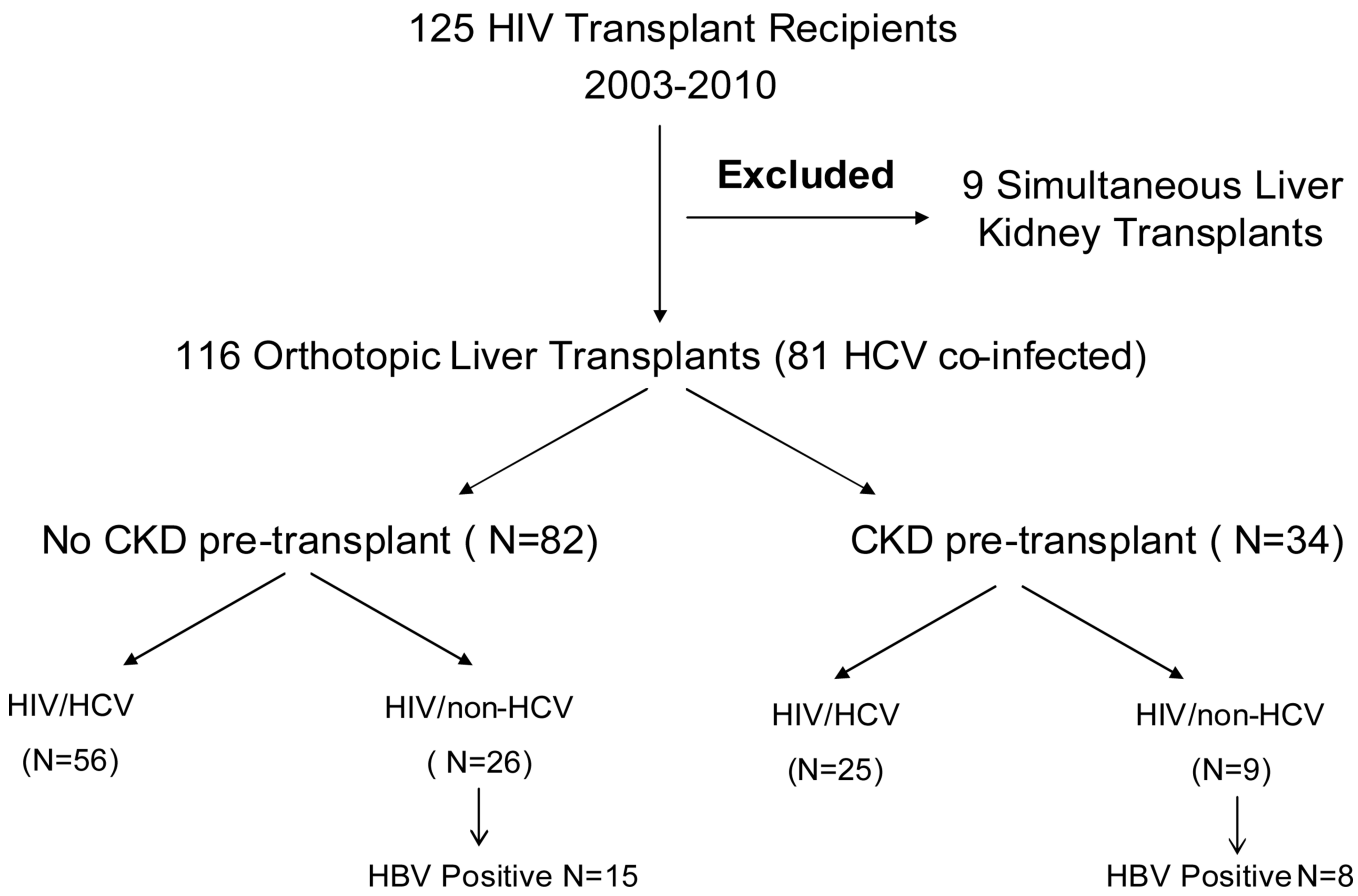

Figure 1.
Patient Selection Flow Diagram

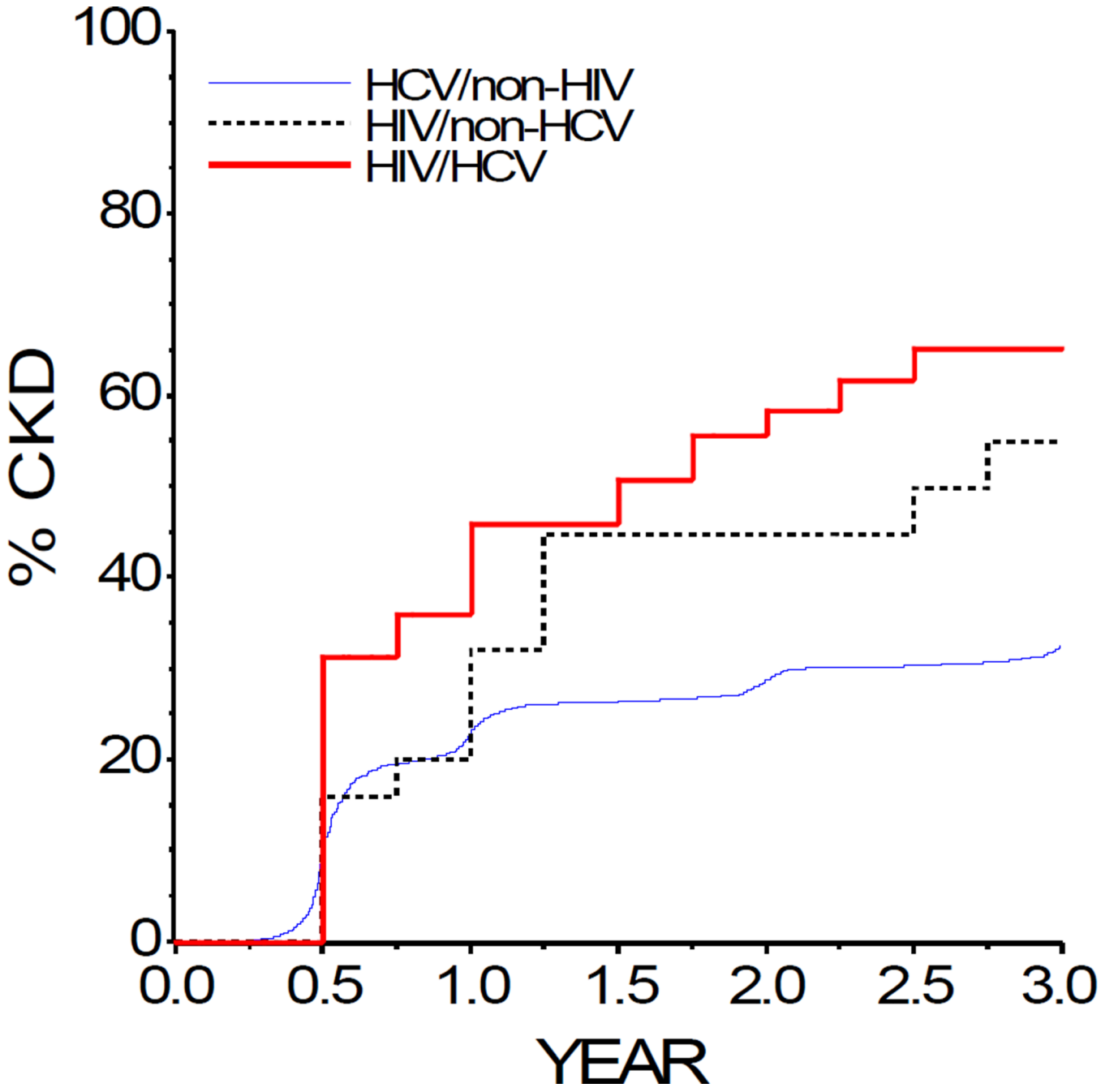

Figure 2.

Kaplan-Meier Estimates of CKD post-OLT by HIV and HCV Infection Status

1 year cumulative incidence of CKD: 36% in HIV/HCV, 20% in HIV/non-HCV and 23% in HCV/non-HIV

3 year cumulative incidence of CKD: 65% in HIV/HCV, 55% in HIV/non-HCV and 32% in HCV/non-HIV

Cumulative incidence of CKD was significantly lower in HCV/non-HIV compared to HIV/HCV or HIV/non-HCV subjects (log-rank test; p<.0001).

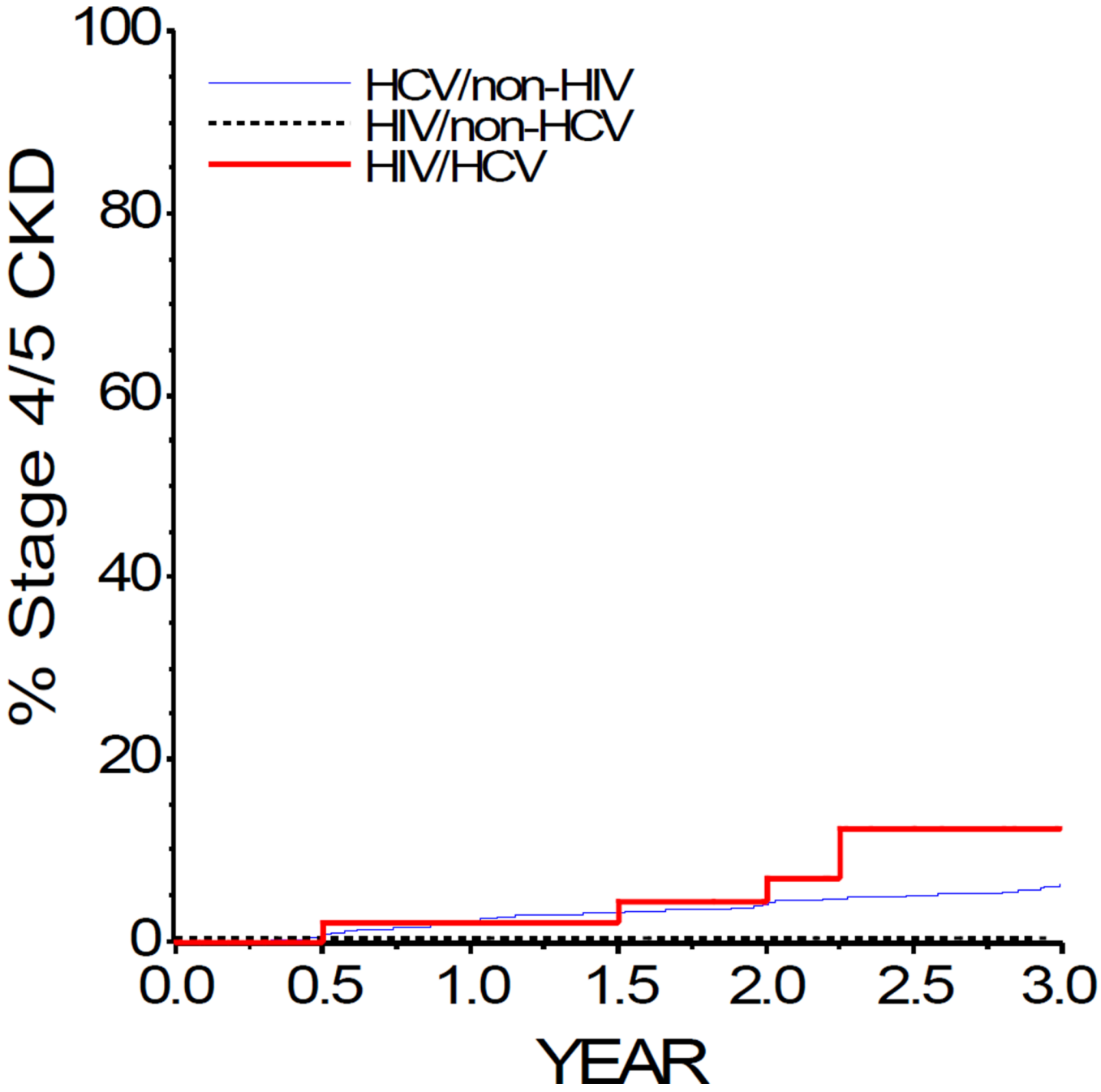

Figure 3.

Kaplan-Meier Estimates of Stage 4/5 CKD post-OLT by HIV and HCV Infection Status

1 year cumulative incidence of Stage 4/5 CKD: 2% in HIV/HCV, 0% in HIV/non-HCV and 2.2% in HCV/non-HIV

3 year cumulative incidence of Stage 4/5 CKD: 12% in HIV/HCV, 0% in HIV/non-HCV and 6.1% in HCV/non-HIV

Cumulative incidence of stage 4/5 CKD was significantly higher in HIV/HCV coinfected subjects compared to HIV/non-HCV or HCV/non-HIV subjects (log-rank test; p=0.001).

Table 1

Characteristics of OLT Recipients without Pre-transplant CKD

	HIV/HCV(N=56)	HIV/non-HCV(N=26)	HCV/non-HIV(N=6594)	P Value
Recipient Characteristics				
Age – yr (median [IQR])	48 [44, 52]	44.5 [42, 50]	54 [50–57]	<.0001
Female Gender – no. (%)	14 (25)	5 (19)	1289 (20)	0.54
Caucasian – no. (%)	35 (63)	20 (77)	4769 (72)	0.24
MELD at OLT (median [IQR])	18 [13–22]	16 [13–30]	15 [11– 20]	0.005
Albumin at OLT – g/dL (median [IQR])	2.7 (2.2– 3.0)	2.9 (2.4–3.4)	N/A	0.11
Pre-OLT eGFR – ml/min (median [IQR])	98 [74– 127]	97 [70–110]	93 [76–113]	0.59
Pre-OLT Diabetes[a] – no. (%)	28 (50)	11 (42)	N/A	0.64
Donor Characteristics				
Donor Age – yr (median [IQR])	43 [23.5, 51.5]	42 [29, 55]	43 [26–53]	0.80
Post-Transplant Characteristics				
Initial calcineurin inhibitor Use – no. (%)				
Cyclosporine	22 (39)	7 (27)		0.56
Tacrolimus	31 (55)	18 (69)		
Neither	3 (5)	1 (4)		
HCV Treatment – no. (%)	24 (43)	N/A		
Treated Acute Cellular Rejection – no. (%)	21 (38)	8 (31)		0.63
CMV Infection – no. (%)	4 (7)	0 (0)		0.30
Proteinuria[b] – no. (%)	10 (18)	2 (8)		0.32
Diabetes[a] – no. (%)	33 (59)	12 (46)		0.34
Hypertension[c] – no. (%)	50 (89)	21 (81)		0.31
Follow-up Post- OLT – yr (median [IQR])	3.5 [2.2, 4.9]	4.4 [2.7, 5.0]		0.12
HIV-Specific Characteristics				
CD4+ T-Cell (cells/mm^3) [d] – median [IQR]	316 [217–471]	347 [172– 490]		0.91
HIV RNA Undetectable [d] – no. (%)	49 (88)	22 (85)		0.74

[a] Based on the use of insulin or any glucose lowering therapy

[b] Based on available lab data at select time points and post-transplant adverse events

[c] Based on the use of anti-hypertensives

[d] At enrollment

Table 2

Cumulative incidence (95% confidence interval) of CKD post-OLT in patients without pre-transplant CKD

Time point		HIV Entire Cohort	HIV/HCV (n=56)	HIV/non-HCV (n=26)	SRTR HCV/non-HIV (n=6594)
1 year	Stage 3 CKD	30% (21–43%)	36% (24–51%)	20% (9– 42%)	23% (22–24%)
	Stage 4/5 CKD	1% (0–9%)	2% (0–14%)	0%	2.2% (1.9–2.7%)
3 year	Stage 3 CKD	62% (50–74%)	65% (50–80%)	55% (36–75%)	32% (31–34%)
	Stage 4/5 CKD	8% (3–18%)	12% (5–28%)	0%	6.1% (5.4–7.0%)

Table 3

Univariate/Multivariate Proportional Hazards Regression Models for CKD

Univariate Predictors	HR (95% CI)	P Value
Pre-transplant eGFR	0.99 (0.98, 1.00)	**0.02**
Age	1.05 (1.01, 1.09)	**0.02**
Gender (Female)	1.09 (0.52, 2.29)	0.82
Race (White)	0.85(0.44, 1.65)	0.64
CD4 at enrollment (per 50 cells/μL)	0.93 (0.85, 1.01)	0.08
Detectable HIV RNA at enrollment	0.60 (0.18, 1.94)	0.39
HCV Infection Status (Positive)	1.44 (0.74, 2.79)	0.28
Most recent MELD pre-OLT	1.00 (0.96, 1.05)	0.89
Diabetes pre-OLT	1.14 (0.61, 2.11)	0.68
Donor Age > 40	1.18 (0.63, 2.22)	0.60
Tacrolimus as Initial immunosuppression	0.58 (0.31, 1.09)	0.09
Treated Acute Cellular Rejection *	0.73 (0.34, 1.60)	0.44
CMV Infection *	§	0.99
HCV Therapy Post-OLT *	0.73 (0.30, 1.82)	0.50
Cyclosporine trough level *	1.00 (1.00, 1.01)	0.70
Tacrolimus trough level *	0.99 (0.90, 1.09)	0.78
Cyclosporine use in prior 3 months *	1.87 (1.01, 3.48)	**0.048**
TDF use in prior 3 months *	0.71 (0.37, 1.38)	0.31
D4T/DDI use in prior 3 months *	1.17 (0.28, 4.96)	0.83
Any PI use in prior 3 months *	0.78 (0.42, 1.44)	0.42
CD4 count (per 50 cells/μL) *	0.90 (0.82, 0.98)	**0.01**
Detectable HIV RNA *	0.72 (0.22, 2.35)	0.59
Proteinuria *	1.46 (0.57, 3.73)	0.43
Diabetes *	1.18 (0.64, 2.19)	0.59
Hypertension *	1.15 (0.48, 2.74)	0.75
Multivariate Predictors	**HR**	**P Value**
CD4 count (per 50 cells/μL) *	0.90 (0.83, 0.98)	**0.01**
Age	1.05 (1.004, 1.09)	**0.03**
Pre-transplant eGFR	0.99 (0.98, 1.001)	0.08

* Time-varying covariate

§ Model did not converge

Table 4

Univariate/Multivariate Proportional Hazards Regression Models for Stage 4/5 CKD

Univariate Predictors	**HR (95% CI)**	**P Value**
Pre-transplant eGFR	0.99 (0.96, 1.01)	0.20
Age	1.09 (1.01, 1.18)	**0.02**
Gender (Female)	3.94 (1.19, 13.1)	**0.03**
Race (White)	0.44 (0.13, 1.44)	0.18
CD4 at enrollment (per 50 cells/μL)	0.90 (0.75, 1.08)	0.24
Detectable HIV RNA at enrollment	§	0.99
HCV Infection Status (Positive)	9.74 (1.22, 77.8)	**0.03**
Most recent MELD pre-OLT	1.02 (0.94, 1.11)	0.68
Diabetes pre-OLT	1.01 (0.31, 3.32)	0.99
Donor Age > 40	0.51 (0.15, 1.76)	0.29
Tacrolimus as Initial immunosuppression	0.62 (0.17, 2.33)	0.48
Treated Acute Cellular Rejection *	2.64 (0.80, 8.71)	0.11
CMV Infection *	§	1.00
HCV Therapy Post-OLT *	1.75 (0.49, 6.23)	0.39
Cyclosporine trough level *	1.00 (0.99, 1.01)	0.53
Tacrolimus trough level *	1.02 (0.88, 1.19)	0.81
Cyclosporine use in prior 3 months *	1.50 (0.46, 4.95)	0.50
TDF use in prior 3 months *	0.56 (0.17, 1.84)	0.34
D4T/DDI use in prior 3 months *	§	0.99
Any PI use in prior 3 months *	0.36 (0.10, 1.23)	0.10
CD4 count (per 50 cells/μL) *	0.87 (0.73, 1.03)	0.11
Detectable HIV RNA *	1.37 (0.17, 10.8)	0.77
Proteinuria *	3.16 (0.91, 10.9)	0.07
Diabetes *	0.87 (0.27, 2.86)	0.82
Hypertension *	0.92 (0.20, 4.26)	0.91
Multivariate Predictors	**HR**	**P Value**
HCV Infection Status (Positive)	10.8 (1.30, 89.4)	**0.03**
Age	1.12 (1.01, 1.25)	**0.03**

* Time-varying covariate

§ Model did not converge