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The Impact of Hepatitis C Virus Co-infection on HIV-Related Kidney Disease: A Systematic Review and Meta-analysis

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Abstract

In the era of antiretroviral therapy, non-AIDS complications such as kidney disease are important contributors to morbidity and mortality.

Objective—To estimate the impact of hepatitis C co-infection on the risk of kidney disease in HIV patients.

Design/ Methods—Two investigators identified English-language citations in MEDLINE and Web of Science from 1989 through July 1, 2007. References of selected articles were reviewed. Observational studies and clinical trials of HIV-related kidney disease and antiretroviral nephrotoxicity were eligible if they included at least 50 participants and reported hepatitis C status. Data on study characteristics, population, and kidney disease outcomes were abstracted by two independent reviewers.

Results—After screening 2,516 articles, twenty-seven studies were eligible and 24 authors confirmed or provided data. Separate meta-analyses were performed for chronic kidney disease outcomes (n=10), proteinuria (n=4), acute renal failure (n=2), and indinavir toxicity (n=5). The pooled incidence of chronic kidney disease was higher in patients with hepatitis C co-infection (6.2% versus 4.0%; RR 1.49, 95% CI 1.08–2.06). In meta-regression, prevalence of black race and the proportion of patients with documented hepatitis C status were independently associated with the risk of chronic kidney disease. The relative risk associated with hepatitis C co-infection was significantly increased for proteinuria (1.15; 95% CI 1.02–1.30) and acute renal failure (1.64; 95%

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CI 1.21–2.23), with no significant statistical heterogeneity. The relative risk of indinavir toxicity was 1.59 (95% CI 0.99–2.54) with Hepatitis C co-infection.

Conclusions—Hepatitis C co-infection is associated with a significant increase in the risk of HIV-related kidney disease.

Introduction

Infection with the human immunodeficiency virus (HIV) affects more than 30 million people worldwide [1]. In the era of effective antiretroviral therapy, progression to acquired immunodeficiency syndrome (AIDS) is less common, and non-AIDS complications such as kidney disease have become significant contributors to morbidity and mortality [2]3. From 1999–2003, there were more than 4,000 new cases of end-stage renal disease attributed to HIV in the United States [4], primarily in African-Americans [5,6]. With improvements in the survival of HIV-infected dialysis patients [7] and increasing prevalence of HIV infection among African-Americans, the prevalence of HIV-related end-stage renal disease continues to rise [8]. The increased recognition of kidney disease as an important non-AIDS complication is evident in the recent publication of consensus guidelines for the detection and management of chronic kidney disease in patients with HIV [9].

Hepatitis C virus (HCV) co-infection is another increasingly important cause of morbidity and mortality in patients with HIV [2]10, and affects approximately 30% of HIV-infected individuals. [11] Studies have demonstrated that co-infection with HIV and HCV translates into higher morbidity and mortality related to end-stage liver disease. [12] Definitive studies of the impact of HIV-HCV co-infection on kidney disease are lacking, although expert guidelines include HCV co-infection as a possible risk factor for kidney disease [9]. In the general population, studies of the impact of HCV infection on the risk for kidney disease have produced inconsistent results. Data from the United States Veterans Affairs Medical System support an association between HCV infection and risk for end-stage renal disease.[13] In contrast, nationally representative data from the National Health and Nutrition Examination Survey (NHANES) suggest a negative association between HCV infection and early declines in kidney function, and only a weak association between HCV infection and increased risk for proteinuria. [14] While some smaller cohorts have demonstrated an increased risk of kidney disease outcomes associated with HIV-HCV co-infection, [15]16 others have failed to find a significant association, [17]18 or have even suggested a decreased risk in co-infected patients. [19]20

Both HIV and HCV have been implicated in the pathogenesis of specific glomerular diseases [21], and both viruses have been associated with immune dysregulation [22] and diabetes mellitus [23]2425, which may contribute to the development of comorbid kidney disease. In addition, complex antiviral regimens for HIV and HCV often include medications with nephrotoxic potential. [9]2627 With the disproportionate burden of HIV-HCV coinfection in minority populations at increased risk of kidney disease, [11] identification of HCV co-infection as a risk factor for kidney disease would have significant implications for public health and for clinical care. We conducted a systematic review of the literature to identify studies of kidney disease in HIV-infected patients with known HCV status, and performed a meta-analysis of available data to estimate the impact of HCV co-infection on the risk of kidney disease in patients with HIV.

Methods

This work was performed in accordance with published guidelines for systematic review, analysis, and reporting for meta-analyses of observational studies. [28]

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Literature Review and Study Selection

Two authors independently reviewed English-language citations from the MEDLINE database from 1989 through July 1, 2007, using the search terms “HIV” or “AIDS” and “renal” or “kidney” or “nephropathy.” Data on HCV status were not available prior to 1989, when the first assay for HCV antibodies was described. [29] An additional search was conducted to identify studies of renal adverse events associated with antiretroviral therapy, using the search terms “antiretroviral” or “indinavir” or “tenofovir” and “renal” or “kidney” or “toxicity.” MEDLINE searches were limited to human studies. A second database search was performed via the Science Citation Index Expanded on the Web of Science, and the references of all selected articles were reviewed to identify any additional studies.

Observational studies of kidney disease in HIV-infected patients were selected for further review if the study included at least 50 subjects and collected data on HCV status. Clinical trials and observational studies of the antiretroviral agents indinavir and tenofovir were included if data on renal adverse events and HCV status were reported. Nephrology referral cohorts and biopsy series were excluded unless they described kidney disease prevalence in the source population or included data on kidney disease progression. Because of the low prevalence of HCV infection in children, pediatric studies were not included. Unpublished studies and abstracts were not considered for inclusion in this meta-analysis. Data on study design, study period, patient characteristics, HCV prevalence, and kidney disease outcomes were abstracted by two independent reviewers. All authors of selected articles were contacted to obtain missing data and to confirm published results. Authors were asked to confirm or provide data on the age of the study population, the proportion with documented HCV status and the method used to determine HCV status (HCV antibody or RNA testing), the prevalence of black race, and the distribution of kidney disease endpoints among subjects with and without HCV co-infection, including only those subjects with documented HCV status.

Manuscript quality was assessed using criteria adapted from Hayden et al. [30] Eligible studies were included in the meta-analysis if adequate data on renal outcomes were available from published results or provided by the study author. Only data from subjects with known HCV status were included in the meta-analysis.

Statistical Analysis

We assessed several kidney disease outcomes in patients with HIV-HCV co-infection compared to outcomes in patients with HIV alone in stratified 2×2 contingency tables. We pooled outcomes based on clinical and biological grounds; for example, doubling of serum creatinine in a longitudinal study was considered a “chronic kidney disease” outcome. Overall results for each type of outcome were mathematically pooled using techniques that accounted for within and between study heterogeneity (random effects method of DerSimonian and Laird). [31] We formally assessed heterogeneity of treatment effects among studies with the Cochran Q and the I^2 statistics. [32] To examine the association of study-level characteristics and treatment effect, we fitted random-effects meta-regression models to the natural logarithm of the relative risks by using the PROC GLM procedure in SAS statistical software, version 9.1 (SAS Institute, Cary, North Carolina). We performed subgroup analyses of the factors that were significantly associated with the risk of renal outcomes in the meta-regression models. Publication bias was assessed by examination of funnel plots. All meta-analyses were performed using Comprehensive Meta Analysis 1.0.25 (Englewood, NJ).

Results

We identified 3,219 citations meeting our MEDLINE search criteria. After excluding review articles, 2,513 abstracts were evaluated, and 121 articles were selected for further review

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(Figure 1). Twenty-seven articles met our criteria for inclusion in the summary table, including 22 articles with adequate data for inclusion in our meta-analysis. [33]19[34][35][36][37][38][39]40[41] 17[42][43][44][45][46][47][48]20[49][50][51]15[52][53]18[54] Two of the eligible papers reported outcomes from the same cohort [40]41; therefore, a total of 21 studies were included in the pooled analyses (Table 1–Table 2). Only 18 studies provided a clear definition of HCV co-infection, and only one study required HCV RNA testing for diagnosis. [53] Thirteen of 20 longitudinal studies did not include any information on patient attrition, and only one described the characteristics of patients lost to follow-up. Fifteen studies reported data on age, race, antiretroviral use, and CD4 cell count, although only five studies accounted for all four important potential confounders in their analyses.

Study and patient characteristics from the selected articles are summarized in Table 1. The majority of studies were performed in the United States or Western Europe. Several different study designs are represented, most commonly prospective (n=14) and retrospective cohort studies (n=6). Sixteen studies were performed after the widespread introduction of effective combination antiretroviral therapy in 1996, and 11 studies spanned the years before and after 1996. Among the 19 studies that provided complete data on race, the prevalence of black race ranged from 1%–89%. The prevalence of documented HCV co-infection ranged from 3%–58.1% across studies.

The most frequently measured kidney disease outcomes (Table 2) included longitudinal measures of progression (time to end-stage renal disease, doubling of serum creatinine, decline in creatinine clearance) and cross-sectional measures of laboratory abnormalities (microalbuminuria, proteinuria, or elevated serum creatinine). Other studies analyzed the incidence of treatment-associated renal adverse events, the prevalence of documented acute or chronic kidney disease, and the incidence or prevalence of specific kidney diseases (HIV-associated nephropathy and hemolytic uremic syndrome). One study evaluated the frequency of hospitalization for kidney disease. Several studies contributed data on more than one kidney disease outcome, [15]40,[41]48 but each cohort was only represented once in any meta-analysis. The authors of 24 studies provided additional information and/or confirmed abstracted data, including age of the study population, the proportion with documented HCV status, the method used to determine HCV status, the prevalence of black race, and the distribution of kidney disease endpoints among subjects with and without HCV co-infection.

Chronic Kidney Disease

Twelve studies provided data on the prevalence, incidence, or progression of chronic kidney disease in patients with HCV co-infection, including HIV-associated nephropathy. [19]40[17] [43][44][46]20[50][51]15[52]18 Ten studies with adequate data were included in the meta-analysis, representing more than 14,000 individuals with HIV infection (Figure 2). The definition of chronic kidney disease varied among studies, but was most commonly based on an elevation in serum creatinine or a decrease in creatinine clearance (n=4). One additional study described a combined endpoint of elevated serum creatinine or proteinuria, and 4 studies described the prevalence or incidence of a documented renal diagnosis. A single study of incident HIV-associated nephropathy was also included in this group. The absolute incidence of chronic kidney disease in patients without HCV co-infection ranged from < 1% to 16.9% (pooled incidence 4.0%) and in patients with HCV co-infection ranged from 1.7 to 25.1% (pooled incidence 6.2%). The pooled relative risk of chronic kidney disease in patients with HIV-HCV co-infection compared to those without HCV co-infection was 1.49 (95% CI 1.08–2.06), with some evidence of statistical heterogeneity (Q=24.0, P=0.004, I^2 = 62.5%).

Only three studies provided adjusted estimates of the chronic kidney disease outcomes in patients with HCV co-infection (Table 2). One study reported age-adjusted estimates, [18] while two studies adjusted for age, race, antiretroviral use, and severity of HIV disease. [46]52 The

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association between HCV co-infection and progression of chronic kidney disease remained highly significant in one study (adjusted HR 2.6; 95% CI 1.26–5.37), [52] which was not included in meta-analysis because of unavailable data. In the other two cohorts, there was a strong trend towards an association between HCV co-infection and chronic kidney disease in adjusted analyses.

Proteinuria

Four studies reported the prevalence of proteinuria in patients with HIV-HCV co-infection, totaling 3,588 individuals with HIV infection. Two studies defined proteinuria by standard dipstick urinalysis, one study described the prevalence of microalbuminuria, and one study defined significant proteinuria as a 24-hour urine protein excretion of at least 1.5 grams. The pooled prevalence of proteinuria in patients without HCV co-infection was 19.3%, compared to 28% in patients with HCV co-infection (Figure 2). The pooled relative risk of proteinuria in patients with HIV-HCV co-infection compared to those without HCV co-infection was 1.15 (95% CI 1.02–1.30). There was no evidence of substantial statistical heterogeneity (Q=1.9, P=0.59, I^2 = 0%). Only one study reported an adjusted odds ratio for HCV co-infection. After adjusting for age, race, antiretroviral use, and CD4 cell count, HCV co-infection remained associated with a modest increase in the odds of proteinuria in that study (adjusted OR 1.27, 95% CI 1.16–1.35). [15]

Antiretroviral nephrotoxicity

Eight studies addressed nephrotoxic or urologic complications of antiretroviral agents, primarily tenofovir (n=3) [39,49,54] and indinavir (n=4). [35,36,37,47,48] One study evaluated the incidence of adverse drug events in patients initiating therapy containing any protease inhibitor, and data on renal adverse events were provided by the authors [37]. Additional data were provided for two studies of tenofovir toxicity; [39,49] however, adequate data for meta-analysis were only available for one study. [49] None of the three studies demonstrated an association between HCV co-infection and increased risk for tenofovir nephrotoxicity (Table 2), although pooled analysis was not possible.

Data were available for meta-analysis for all five studies involving indinavir or other protease inhibitors (Figure 2). [35,36,47,48] The absolute incidence of renal or urologic complications in patients without HCV co-infection ranged from 2 to 21% (pooled incidence 9.8%) and in patients with HCV co-infection ranged from 4 to 46% (pooled incidence 15.7%). The pooled relative risk of indinavir toxicity in patients with HIV-HCV co-infection compared to those without HCV co-infection was 1.59 (95% CI 0.99–2.54). There was some evidence of statistical heterogeneity (Q=8.2, P=0.08, I^2 = 51.3%).

Acute Renal Failure

Two studies focused on the incidence of acute renal failure in patients with HIV (Figure 2). Both studies used criteria based on an acute rise in serum creatinine relative to baseline values. The absolute incidence of acute renal failure in patients without HCV co-infection was 8% in an ambulatory cohort [38] and 43% in critically ill patients [45] (pooled incidence 12.5%), and risk of acute renal failure in patients with HCV co-infection was 15% and 65%, respectively (pooled incidence 20.6%). The pooled relative risk of acute renal failure in patients with HIV-HCV co-infection compared to those without HCV co-infection was 1.64 (95% CI 1.21–2.23; Q=0.37, P=0.54, I^2 = 0%). In both studies, the association between HCV co-infection and acute renal failure remained significant in multivariate analysis (Table 2).

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Meta-regression and Subgroup Analyses

Meta-regression was used to identify study-level factors that may have contributed to the statistical heterogeneity observed in pooled analyses of chronic kidney disease and indinavir-related outcomes. For studies examining chronic kidney disease, two study-level factors were significantly associated with the relative risk of chronic kidney disease. These factors were the percentage of individuals with confirmed HCV status (p=0.01) and the percentage of black patients in the cohort (p=0.004). For studies examining indinavir-related toxicity, no study-level factor was associated with the demonstrated effect.

We performed two subgroup analyses based on the results of our meta-regression. Only three studies exploring chronic kidney disease outcomes documented HCV status in 100% of subjects. [43] 15 18 The pooled relative risk in these 3 studies was 1.59 (95% CI 0.98–2.57), with less statistical heterogeneity compared to the pooled analysis of all 10 studies (Q=3.68, p=0.16, I^2 =46%). Pooled analysis of the studies without universal documentation of HCV status yielded a similar point estimate (pooled RR 1.37, 95% CI 0.8–2.37; Q=16.32, p=0.006). For the second study-level factor, the regression line demonstrated that there was an increased relative risk of chronic kidney disease in studies with more than 25% black subjects. A separate meta-analysis including the 7 studies with a higher prevalence of black race (>25%) demonstrated a pooled relative risk of 1.72 for chronic kidney disease in patients with HCV co-infection (95% CI 1.33–2.23; Q=8.6, p=0.2, I^2 = 30%). In contrast, HCV co-infection was not associated with increased risk of chronic kidney disease in pooled analysis of the three studies with a lower prevalence of black race (pooled RR 0.75, 95% CI 0.53–1.07; Q=0.51, p=0.77).

Discussion

The results of the current meta-analysis suggest that HIV-HCV co-infection is associated with an increased risk of kidney disease compared to HIV infection alone. In pooled analyses of data from more than 18,000 HIV infected patients, HCV co-infection was associated with an increased risk of chronic kidney disease by nearly 50%, proteinuria by 15%, and acute renal failure by 64%, and with an increased risk for urologic and nephrotoxic complications of the antiretroviral agent indinavir. These findings have important implications for clinical care and for global public health, and they may provide a new impetus for pathogenic studies of kidney disease in patients with HIV and HCV.

The demonstrated association between HCV co-infection and risk for acute and chronic kidney disease supports existing guidelines for the diagnosis and management of kidney disease in patients with HIV. [9] These consensus guidelines consider HCV co-infection a risk factor for kidney disease, and recommend increased frequency of screening for proteinuria and decline in glomerular filtration rate. Timely recognition of kidney disease may allow targeted therapy to delay progression, and is essential to guide selection and dosing of antiretroviral medications. The impact of HCV co-infection on the risk for antiretroviral nephrotoxicity has not been well described, in part because data on HCV status have not been routinely reported in clinical trials of the relevant agents. Available data do not suggest an increased risk for tenofovir nephrotoxicity in patients with HCV co-infection, although future studies should be encouraged to collect and report data on HCV status. [39,49,54] The results of the current meta-analysis demonstrate a trend towards increased risk of nephrotoxic/urologic complications of indinavir in patients with HIV-HCV co-infection. Although indinavir has been largely replaced by newer protease inhibitors in the United States and Western Europe, it is still commonly used in Africa, Asia, and Eastern Europe, regions with increased HCV seroprevalence. [55] Since the prevalence of HIV-HCV co-infection varies widely based on the primary mode of HIV transmission,[11] the local prevalence of HCV co-infection may be an important consideration in the choice of appropriate antiretroviral regimens for use in resource-limited settings.

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While this is the first quantitative review to address this important clinical question, systematic reviews have a number of inherent limitations. Most importantly, this review is limited by heterogeneity in the design and quality of the available studies. The majority of longitudinal studies did not adequately describe study attrition, and the inclusion of cross-sectional studies limits the ability to establish temporal relationships. The prevalence and impact of important potential confounders were not reported in all studies; in particular, data on race were missing from six studies, primarily from studies conducted in Europe and Australia. The prevalence of black race is likely to be lower in these study populations, which may significantly decrease the background risk of kidney disease [20 5,6,56]. A sensitivity analysis excluding studies with a prevalence of black race below 25% yielded qualitatively similar results, with noticeably less statistical heterogeneity. In addition to the variability in race, there was also significant variability in the kidney disease outcomes measured in the individual studies, and it is possible that HCV co-infection has heterogeneous effects. For example, black race is strongly associated with HIV-related chronic kidney disease and end-stage renal disease [6 4 5], but does not appear to be a risk factor for acute renal failure in patients with HIV [16,57]. HCV co-infection may also have heterogeneous effects on different renal outcomes, including the diverse endpoints considered together as chronic kidney disease in the current analysis. Of interest, the effect size was similar for studies of chronic kidney disease and acute renal failure, although this conclusion is limited by the inclusion of only 2 studies of acute renal failure. Another important limitation of the current study involves the assessment of HCV status. The proportion of study subjects with documented HCV status ranged from 42%–100% across studies, with universal documentation of HCV status in fewer than half of the studies. Although only data from subjects with known HCV status were included in the current meta-analysis, the lack of universal HCV screening may have biased our study population. Comparisons between subjects with and without documented HCV status were not possible based on study-level data.

Few of the studies included in the current meta-analysis provided adjusted estimates of the risk for kidney disease associated with HCV co-infection. The observed association between HCV co-infection and increased risk for kidney disease could reflect confounding by other factors, such as older age, black race, history of injection drug use, or exposure to nephrotoxic medications. Data on potential mediators such as diabetes, cryoglobulinemia, and end-stage liver disease were also not reported in most studies. In conclusion, HCV coinfection in HIV-positive patients is associated with an increased risk of kidney disease. Health care providers should be aware of this risk, and future studies should investigate the mechanism of the observed association to allow for targeted interventions in susceptible patients. In the interim, patients with HIV-HCV co-infection should be regarded as being at increased risk for acute and chronic kidney disease, regardless of the presence of traditional kidney disease risk factors.

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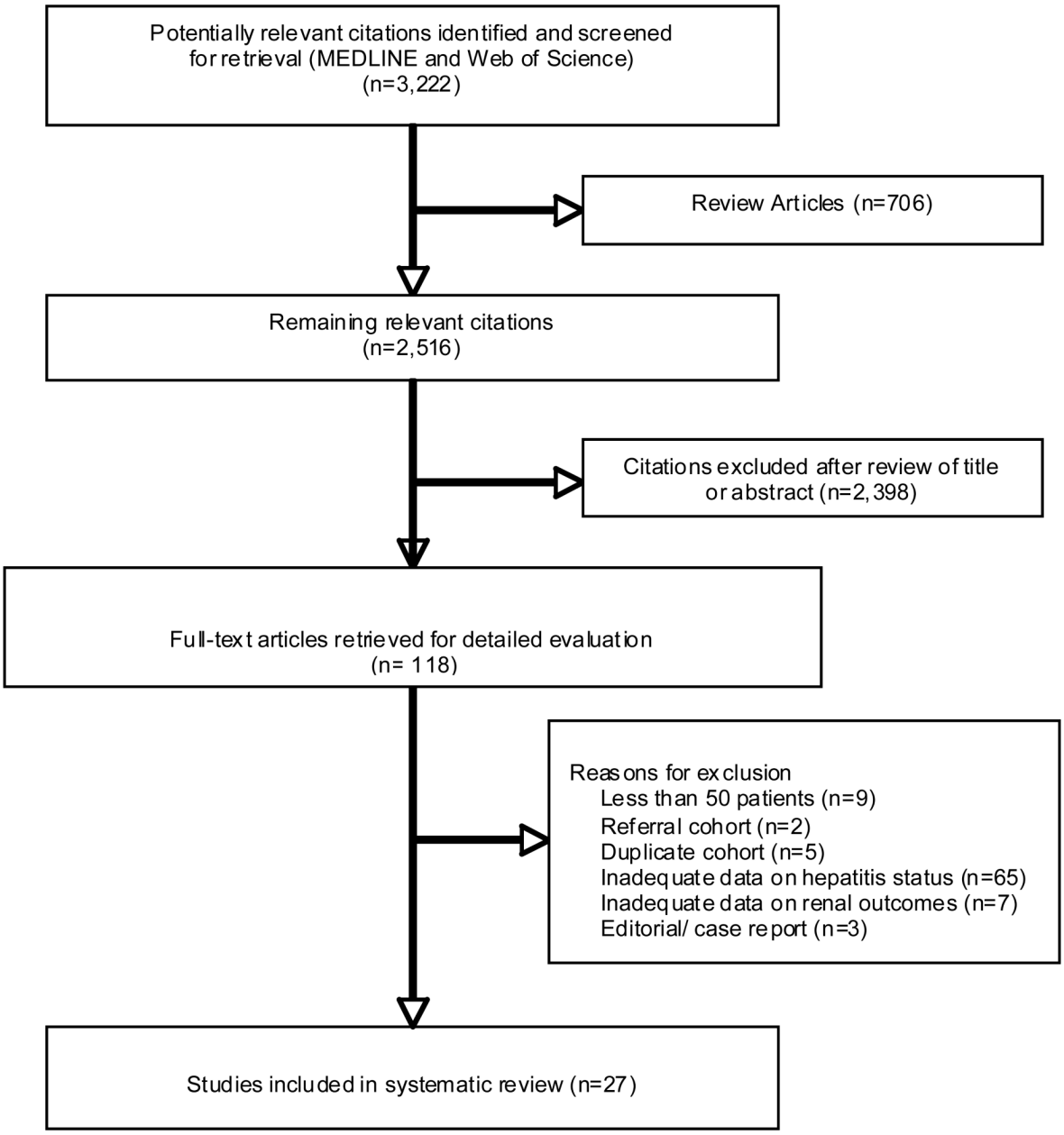

Figure 1.
Flow diagram of studies of HIV-related kidney disease considered for inclusion.

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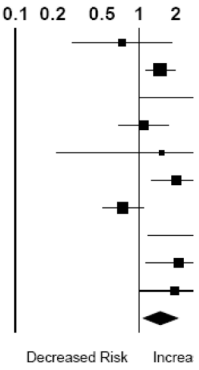
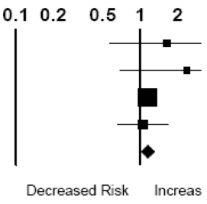
Chronic Kidney Disease Outcomes

	Citation	Hepatitis C	No Hepatitis C	RandomWtPct	Effect	Lower	Upper
	Bagnis et al, 2006	5 / 173	30 / 756	7.35	.73	.29	1.85
	Gardner et al, 2003a	135 / 537	57 / 337	16.47	1.49	1.13	1.96
	Gupta et al, 2004	5 / 66	4 / 189	4.75	3.58	.99	12.93
	Krawczyk et al, 2004	18 / 83	62 / 311	13.52	1.09	.68	1.73
	Kulkarni et al, 2003	23 / 481	1 / 32	2.37	1.53	.21	10.97
	Lucas et al, 2004	55 / 1544	25 / 1416	13.49	2.02	1.26	3.22
	Mocroft et al, 2007	32 / 922	135 / 2875	14.94	.74	.51	1.08
	Reisler et al, 2003	5 / 292	6 / 1336	5.38	3.81	1.17	12.41
	Szczech et al, 2002	25 / 804	17 / 1152	11.27	2.11	1.15	3.88
	Tedaldi et al, 2003	16 / 267	17 / 556	10.45	1.96	1.01	3.82
Random	**Combined (10)**	**319 / 5169**	**354 / 8960**		**1.49**	**1.08**	**2.06**



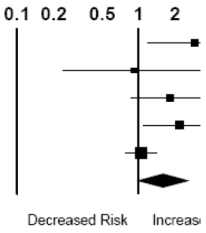
Proteinuria

	Citation	Hepatitis C	No Hepatitis C	RandomWtPct	Effect	Lower	Upper
	Ahuja et al, 1999	5 / 130	10 / 427	1.27	1.64	.57	4.72
	Jung et al, 2004	2 / 7	25 / 207	.94	2.37	.69	8.07
	Szczech et al, 2002	301 / 854	370 / 1203	91.50	1.15	1.01	1.30
	Szczech et al, 2007	20 / 176	63 / 584	6.29	1.05	.66	1.69
Random	**Combined (4)**	**328 / 1167**	**468 / 2421**		**1.15**	**1.02**	**1.30**



Indinavir Toxicity

	Citation	Hepatitis C	No Hepatitis C	RandomWtPct	Effect	Lower	Upper
	Brodie et al, 1998	10 / 27	6 / 47	16.18	2.90	1.19	7.10
	Dieleman et al, 2003	2 / 11	13 / 65	9.30	.91	.24	3.49
	Duval et al, 2004	11 / 274	17 / 770	19.72	1.82	.86	3.83
	Malavaud et al, 2001	6 / 13	21 / 99	20.98	2.18	1.08	4.38
	Meraviglia et al, 2002	62 / 256	69 / 299	33.82	1.05	.78	1.42
Random	**Combined (5)**	**91 / 581**	**126 / 1280**		**1.59**	**.99**	**2.54**



Acute Renal Failure

	Citation	Hepatitis C	No Hepatitis C	RandomWtPct	Effect	Lower	Upper
	Franceschini et al, 2006	24 / 160	45 / 545	44.22	1.82	1.14	2.89
	Lopes et al, 2007	13 / 20	33 / 77	55.78	1.52	1.00	2.29
Random	**Combined (2)**	**37 / 180**	**78 / 622**		**1.64**	**1.21**	**2.23**

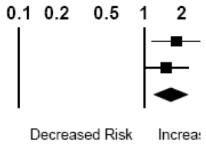


Figure 2.
Pooled Analysis of Kidney Disease Outcomes

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Table 1

Characteristics of Studies of HIV-Related Kidney Disease Outcomes

Source	Country	# of patients	Years of enrollment	Study type	Age, years	HCV % Known	HCV % Positive	Black race, %	Male, %
Ahuja et al 1999	United States	557	1998	CS	37	100	23.3	50.0	79.7
Bagnis et al, 2006	France	1219	2001	CS	42	78.8	14.2	NA	76.1
Becker et al, 2004	United States	6022	1997–2003	PC	43	NA	11.4	14.9	90.9
Brodie et al, 1998	United States	79	1995–1997	RC	NA	93.7	34.2	NA	60.8
Dieleman et al, 2003	Netherlands	184	1998–2000	PC	41	41.8	6.0	NA	81.3
Duval et al, 2004	France	1155	1997–1999	PC	36	90.4	23.7	NA	77
Franceschini et al, 2006	United States	705	2000–2002	PC	40	100	22.7	61.0	68.7
Gallant et al, 2005	United States	658	2001–2003	RC	38	NA	36.9	73.7	71.6
Gardner et al, 2003_a	United States	885	1993–2000	PC	NA	98.8	56.3	60.8	0
Gardner et al, 2003_b	United States	885	1993–2000	PC	NA	98.8	56.3	60.8	0
Gupta et al, 2004	United States	487	1990–1998	RC	34	52.4	13.6	52.4	81.5
Jung et al, 2004	Germany	214	2001–2002	PC	42	100	3.3	2.3	89.7
Krawczyk et al, 2004	United States	394	1992–2002	CC	43	100	21.1	48.0	82.2
Kulkarni et al, 2003	United States	828	1993–1998	RC	31	62	58.1	23.8	100
Lopes et al, 2007	Portugal	97	2002–2006	RC	43	100	20.6	28.9	79.4
Lucas et al, 2004	United States	3976	1989–2001	PC	37	74.5	52	77.0	70
Malavaud et al, 2001	France	112	1998	CC	40	100	11.6	NA	73.2
Meraviglia et al, 2002	Italy	555	1997	PC	38	100	46.1	1.4	77.1
Mocroft et al, 2007	Europe	4474	2004–2005	CS	43	84.9	20.6	14.5*	76.1

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Source	Country	# of patients	Years of enrollment	Study type	Age, years	HCV % Known	HCV % Positive	Black race, %	Male, %
Padilla et al, 2005	Spain	316	2001–2003	CC	40	54.7	32.0	1.3	76.0
Reisler et al, 2003	United States	2947	1996–2001	PC	39	55.2	9.9	44.8	83.0
Shahinian et al, 2000	United States	389	1992–1997	CS	40	47.8	20.6	54.0	93.1
Szczech et al, 2002	United States	2057	1994–1999	PC	37	100	41.5	55.5	0
Szczech et al, 2004	United States	89	1995–2001	RC	42¶	92.1	47.2	88.8	82.0
Szczech et al, 2007	United States	760	1999	CS	44	100	23.2	44.0	73.7
Tedaldi et al, 2003	United States	823	1996–2001	PC	37¶	100	32.4	64.3*	NA
Winston et al, 2006	Australia	948	2005	PC	45¶	NA	7.1	NA	95.8

Abbreviations **CS**, Cross-sectional, **PC**, Prospective cohort, **RC**, Retrospective cohort, **CC**, case control, **HCV**, Hepatits C virus status, **NA**, Not available

¶ weighted average

* Non-white race; all percentages represent the proportion of the total study population

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Table 2

Kidney Disease Outcomes in Patients with HIV and HIV-Hepatitis C Co-Infection.

			Outcomes, %		Reported Effect Size		
Source	**Outcome Definition**	**Length of f/u**	**HCV**	**No HCV**	**Univariate**	**Adjusted**	**Attrition**
Ahuja et al	Proteinuria > 1.5g/day	…	3.9	2.3	1.7 (0.4–5.5)	NA	…
Bagnis et al	↑creatinine	…	2.9	4.0	↓creatinine	NA	…
Becker et al	Hemolytic uremic syndrome	Median 4.1 yrs	0.7	0.2	NA	NA	13%
Brodie et al	Nephrolithiasis (IDV)	2 yrs	37.0	12.8	4.0 (1.1–15.5)	4.0	NA
Dieleman et al	Pyuria (IDV)	Median 48 wks	18.2	20.0	NS	NA	NA
Duval et al	Renal SAE (PI)	Median 1.9 yrs	4.0	2.2	NA	NA	NA
Franceschini et al	Acute renal failure	2 yrs	15.0	8.3	*	*	NA
Gallant et al	Δ creatinine clearance (TDF)	Median 1 yr	Δ −9%	Δ −8%	NS	NA	NA
Gardner et al[a]	↑creatinine or proteinuria	21 mos	25.1	16.9	NA	NA	NA
Gardner et al[b]	Renal hospitalization	21 mos	9.4	3.5	NA	1.7 (.05–5.5)	13%
Gupta et al	Doubling of creatinine	5 years	7.6	2.1	3.8 (0.8–19.6)	NA	NA
Jung et al	Persistent proteinuria	12–15 mos	28.6	12.1	NS	NA	17%
Krawczyk et al	Confirmed diagnosis of CKD	4–5.1 yrs	21.7	20.0	1.1 (0.6–2.1)	NS	…
Kulkarni et al	Documented renal diagnosis	6 yrs	4.8	3.1	NA	NA	NA
Lopes et al	Acute renal failure in ICU	Admission	65.0	42.9	NA	3.4 (1.1–10.9)	NA
Lucas et al	Clinical or histologic HIVAN	11,732 pyrs	3.6	1.8	2.0 (1.2–3.4)	1.5 (0.9–2.4)	10%
Malavaud et al	Nephrolithiasis (IDV)	…	46.2	21.2	NS	NA	…
Meraviglia et al	Renal colic (IDV)	24 mos	24.2	23.1	NS	NA	…
Mocroft et al	Creatinine clearance < 60	…	3.5	4.7	NA	NA	…
Padilla et al	Graded creatinine (TDF)	Median 48 wks	2.0	2.8	NS	NA	…
Reisler et al	Renal adverse event	Median 21 mos	1.7	0.5	NS	NA	NA
Shahinian et al	Biopsy diagnosis of HIVAN	…	NA	NA	NS	NA	…
Szczech et al	Proteinuria Doubling of creatinine	5 yrs	35.3 3.1	30.8 1.5	NA NA	1.3 (1.2–1.4) *	19%
Szczech et al	Time to ESRD	NA	NA	NA	NA	2.6 (1.3–5.4)	NA
Szczech et al	Microalbuminuria	…	11.4	10.8	NA	NA	…
Tedaldi et al	Documented kidney disease	2.7–3.1 yrs	6.0	3.1	2.0 (1.0–3.8)	1.8 (0.9–3.6)	13%
Winston et al	Δ creatinine clearance (TDF)	NA	NA	NA	NS	NA	NA

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Abbreviations: **IDV**, indinavir, **PI**, protease inhibitor, **TDF**, tenofovir, **ICU**, intensive care unit, **yrs**, years, **pyrs**, patient years, **…**, not applicable, **NA**, not available, **f/u**, follow-up, **CKD**, chronic kidney disease, **NS**, no significant association

* data available for subgroups