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Changing Trends in the Survival of Dialysis Patients with Human Immunodeficiency Virus in the United States

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Abstract. HIV-infected patients with end-stage renal disease have a very high morbidity and mortality. In the last decade, survival of HIV-infected patients in the United States has remarkably improved. To determine whether similar improvement in survival has occurred in HIV-infected dialysis patients, their survival was evaluated by using the United States Renal Data System database. Survival of HIV-infected dialysis patients in the United States was determined and the influence of year of initiation of dialysis, and demographic characteristics on the survival were analyzed by the Kaplan-Meier method. The effects of above variables on survival were also examined in a Cox proportional hazards model. Identified were 6166 HIV-infected patients with end-stage renal disease who received dialysis in the United States. Eighty-nine percent of the patients were black, 7.4% white, and 3% other. From 1990 to 1999, 1-yr survival of HIV-infected patients on dialysis improved from 56 to 74%, and the annual death rates declined from 458 deaths to 240 deaths per 1000 patient-years. The hazard ratio declined significantly in patients who initiated dialysis in years 1999-2000 compared with patients who initiated dialysis $\leq$ 1990 (hazard ratio, 0.49; 95% confidence interval, 0. 40 to 0.60). Survival of HIV-infected dialysis patients has remarkably improved in the United States.

HIV infection is a common cause of end-stage renal disease (ESRD), especially in blacks, who develop a fulminant form of focal segmental glomerulosclerosis termed HIV-associated nephropathy (HIVAN) or AIDS nephropathy (1–6). HIVAN has become the third most common cause of ESRD in young African Americans (7). Initial reports suggested a very poor prognosis for HIV-infected patients on chronic maintenance dialysis, and it was an ethical dilemma whether these patients should be offered long-term renal replacement therapy (3,8). Although single-center reports have suggested that these patients experience improvements in survival, the mortality and morbidity of HIV-infected dialysis patients remains high (9–14).

In the recent years, use of potent antiretroviral drugs, improved prophylaxis, and treatment of opportunistic infections have led to dramatic improvement in survival of HIV-infected patients (15–17). However, the improved survival of these patients may not extend to the HIV-infected dialysis patients for the following reasons. First, because the pharmacokinetics of the majority of antiretroviral drugs have not been thoroughly evaluated in patients with renal failure, these patients are more likely to be treated with suboptimal antiretroviral therapy. Second, the associated uremia with HIV infection may further impair the immunological response of these already immunocompromised patients, thereby predisposing them to opportunistic infections. Finally, there is a theoretical possibility that hemodialysis may actually increase morbidity of HIV-infected ESRD patients by enhancing viral replication through activation of white blood cells and release of cytokines such as tumor necrosis factor alpha, interleukin 1, and interleukin 6; all of these cytokines have been found to increase viral replication *in vitro* (18–22).

We therefore undertook the study presented here by using the United States Renal Data System (USRDS) database to determine whether the survival of HIV-infected dialysis patients in the United States has improved.

Materials and Methods

Study Patients

The data were obtained from the USRDS Standard analysis files 2000 (SAF.MEDEVID, SAF.PATIENTS, and RxGROUP). The USRDS includes data on approximately 92% of patients receiving dialysis in the United States (23). The accuracy of these data has been validated previously (24). From a database of 1,090,121 patients, HIV-infected patients were identified by the codes 0429A, 0429Z, or 0449Z of the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). Demographic variables used in the analysis include age, gender, and race (black, white, and other). Because dialysis data were available until May 1, 2000, this date was used as a censor date for survival analysis.

Statistical Analyses

The Kaplan-Meier method was used to estimate the survival of HIV-infected dialysis patients. The log rank test was used to compare cumulative survival among these patients stratified by race, gender, and year dialysis was begun. An analysis was also conducted to

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compare survival of HIV-infected ESRD patients with 1000 HIV-negative patients. These patients were randomly selected and were matched for age, gender, race, and year of initiation of dialysis with the HIV-infected patients. A Cox proportional hazards model was used to evaluate the effect of demographic characteristics and year of initiation of dialysis. The reported *P* values in the Cox model are based on the Wald test. All reported *P* values are two-sided. All values are mean ± SD unless otherwise indicated. Statistical analysis was performed with use of SAS system for Windows, version 8e (SAS Institute, Cary, NC). The Human Subject Research Committee of the University of Texas Medical Branch Galveston institutional review board approved this study.

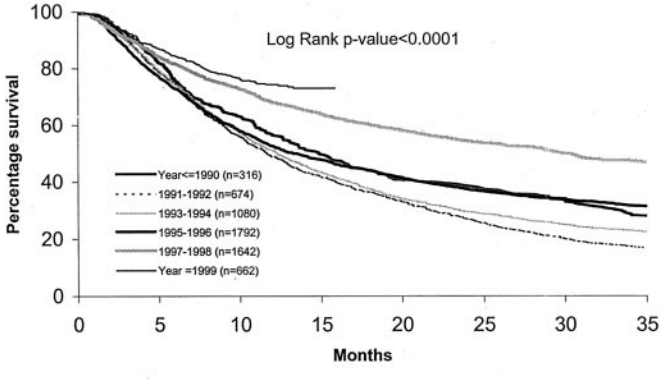
Results

We identified 6179 patients with HIVAN or HIV infection and ESRD by using the USRDS database. Thirteen patients were excluded from the analysis. In 8 of these 13 patients, information available for survival analysis was incomplete, and in 5 patients, renal transplantation was the primary renal replacement therapy. All of the patients included in the study were HIV infected at the time of starting dialysis, and in 99%, the cause of ESRD listed was HIVAN (ICD-9 code 0429A). The first and the last patient included in the study began dialysis in December 1985 and December 1999, respectively. The mean follow-up period of the patients on dialysis was 21 ± 21. 48 mo. The mean age of the patients was 39.4 ± 8.9 yr. Eighty-nine percent of the patients were black, 7.4% were white, and 3.4% were other. Seventy-four percent were men, and 26% were women.

Figure 1 shows Kaplan-Meier estimates of survival of HIV-infected ESRD patients starting dialysis before 1990 and then biyearly until May 2000. The survival rate at 12 and 24 mo of the patients starting dialysis before 1990 improved from 56 and 38% to 68 and 54% compared with patients who started dialysis in the years 1997 to 1998. One-year survival rate of patients who started dialysis in 1999 to 2000 further improved to 74%. Table 1 summarizes the estimated cumulative percent survival of these patients. In contrast to a minimal decline in annual death rates for the HIV-negative dialysis patients, the annual death rates of HIV-infected dialysis patients declined from 458 deaths to 240 deaths per 1000 patient-years from 1990 to 1999 (Table 2). The major improvement in survival of these patients occurred since 1997 (Tables 1 and 2). In the regression model, the only factor associated with a decrease in relative risk of death was later years of initiation of dialysis (hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.81 to 0.85) Table 3.

In another Cox model, we adjusted for the demographic variables and used time as a categorical variable in biyearly periods similar to that in the life-table analysis. In this model, the relative risk for patients starting dialysis in the years 1999 to 2000 was significantly lower (HR, 0.48, 95% CI, 0.40 to 0.50), compared with patients who started dialysis before 1990. The significant change was again seen starting 1997, when the HR of the patients starting dialysis in years 1997 to 1998 declined to 0.60 (95% CI, 0.52 to 0.69) from 0.92 (95% CI, 0.81 to 1.05), the previous biyearly period (1995 to 1996).

Race was not a factor in predicting survival on dialysis (Figure 2 and Table 3). Although female dialysis patients appeared to have better survival than male patients (Figure 3), the survival advantage was lost when the data were adjusted for the demographic variables and year of initiation of dialysis in the regression model (HR, 0.98; 95% CI, 0.91 to 1.05; Table 3). On examination of the residual and global fitness measures



Months →	5	10	15	20	25	30	35
Year<=1990	260	200	157	127	118	104	87
1991-1992	530	377	282	222	172	134	113
1993-1994	859	620	468	369	312	271	244
1995-1996	1383	1040	858	746	659	612	566
1997-1998	1378	1193	1047	797	548	336	169
1999	573	323	51	--	--	--	--

Figure 1. Kaplan-Meier estimates of survival of HIV-infected patients from the start of dialysis from before 1990 and then biyearly until May 2000. The number of patients at various times is shown in the table below the figure.

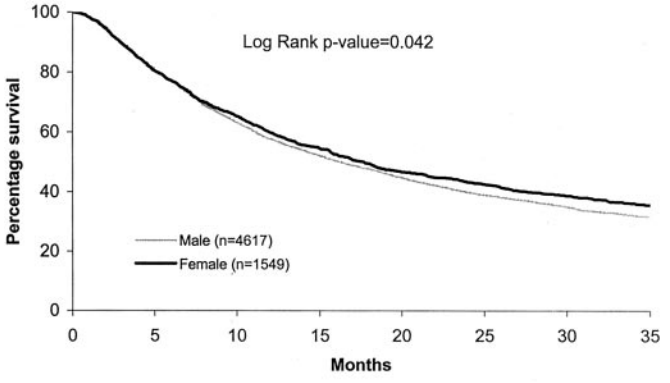
Table 1. Estimated cumulative percentage survival of HIV-infected end-stage renal disease patients on dialysis according to the year of starting renal replacement therapy, gender, race, and dialysis modality[a]

Parameter	12 Months	24 Months	36 Months
Year			
≤1990	56 ± 2.8	38 ± 2.7	27 ± 2.5
1991–1992	49 ± 1.9	27 ± 1.7	17 ± 1.4
1993–1994	51 ± 1.5	30 ± 1.4	22 ± 1.3
1995–1996	53 ± 1.2	38 ± 1.1	31 ± 1.1
1997–1998	68 ± 1.2	54 ± 1.3	47 ± 1.5
1999–2000	74 ± 1.8		
Gender			
male	58 ± 0.7	40 ± 0.8	31 ± 0.8
female	60 ± 1.3	43 ± 1.3	35 ± 1.4
Race			
black	59 ± 0.6	41 ± 0.7	32 ± 0.7
white	54 ± 2.3	40 ± 2.4	31 ± 2.4
other	57 ± 3.7	42 ± 3.8	35 ± 3.9
Dialysis modality			
hemodialysis	59 ± 0.7	41 ± 0.7	33 ± 1.0
home hemodialysis	60 ± 7.8	41 ± 8.0	37 ± 8.1
peritoneal dialysis	56 ± 1.6	50 ± 1.6	29 ± 1.5

[a] Values are expressed as percentage ± SE.

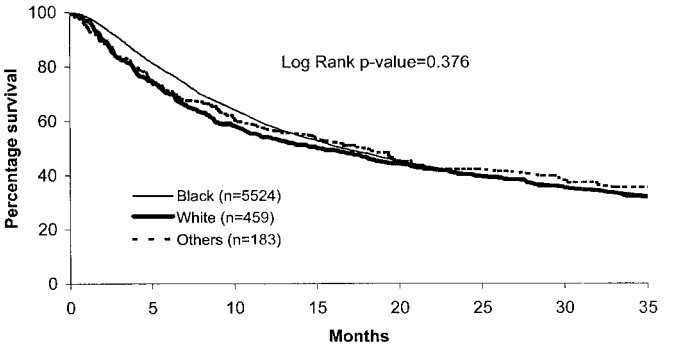
Table 2. Annual death rates for HIV-infected *versus* HIV-negative dialysis patients, period prevalent patients for the year per 1000 patient-years at risk

Year	HIV Infected	HIV Negative
1990	458.6	263.2
1991	407.7	256.6
1992	525.6	265.9
1993	487.8	266.7
1994	605.0	254.9
1995	490.55	251.5
1996	475.2	247.7
1997	291.6	237.3
1998	250.5	230.6
1999	240.2	236.4



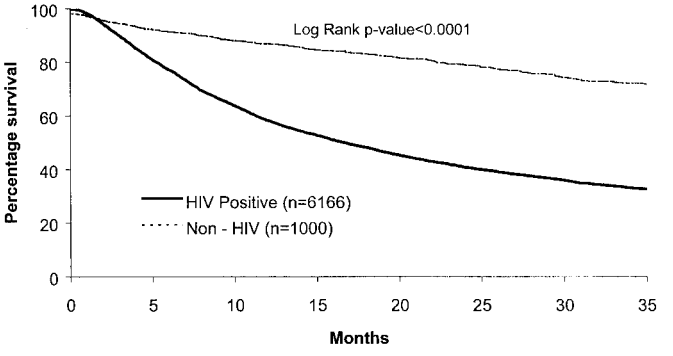
Months→	5	10	15	20	25	30	35
Male	3742	2803	2143	1713	1359	1100	890
Female	1247	954	725	552	452	357	282

Figure 2. Kaplan-Meier estimates of survival of HIV-infected dialysis patients by gender. The number of patients at various times is shown in the table below the figure.



Months→	5	10	15	20	25	30	35
Black	4510	3396	2573	2026	1618	1302	1048
White	343	254	207	172	142	111	95
Others	137	108	89	68	52	45	37

Figure 3. Kaplan-Meier estimates of survival of HIV-infected dialysis patients by race. The number of patients at various times is shown in the table below the figure.



Months→	5	10	15	20	25	30	35
HIV	4990	3758	2869	2266	1812	1458	1180
Non-HIV	922	849	766	707	629	544	477

Figure 4. Kaplan-Meier estimates of survival of HIV-infected patients compared with a matched group of HIV-negative patients. The number of patients at various times is shown in the table below the figure.

for the various Cox models, no evidence of lack of fit or model inadequacy was discovered.

The survival of the random matched group of HIV-negative dialysis patients was significantly better Figure 4. The 12- and 24-mo survival of these patients was 87 and 79%, respectively, compared with 58 and 41% of HIV-infected patients.

Discussion

In the study presented here, we report that the survival of HIV-infected ESRD patients on dialysis in the United States has improved in the recent years. The major improvement in survival has occurred since 1997, when 1- and 2-yr survival of

Table 3. Results of Cox proportional hazards model of survival of HIV-infected dialysis patients ($n = 6166$)

Risk Factor	Hazard Ratio (95% Confidence Interval)			
	Unadjusted	*P* Value	Adjusted	*P* Value
Age	0.99 (0.99–1.00)	0.07	1.00 (0.99–1.00)	0.57
Sex	0.93 (0.86–0.99)	0.04	0.98 (0.91–1.05)	0.60
Race (white *versus* black)	1.08 (0.97–1.21)	0.17	1.06 (0.95–1.19)	0.30
Race (other *versus* black)	0.98 (0.81–1.17)	0.79	1.04 (0.86–1.25)	0.70
Year of initiation/dialysis	0.83* (0.81–0.85)	0.0001	0.83* (0.81–0.85)	0.0001

patients who started dialysis in years 1997 to 1998 improved to 68 and 54% from 52 and 37%, respectively, compared with patients who started dialysis in previous years (1995 to 1996). The 1-yr survival further improved to 74% in the patients who started dialysis in years 1999 to 2000, an 18% increase in 1-yr survival compared with patients who started dialysis before 1990. The annual death rate of HIV-infected patients declined from 458 deaths to 240 deaths per 1000 patient-years. The major improvement has occurred since 1997.

Early reports had described a dismal mean survival of HIV-infected patients with ESRD (3,8). Some small, single-center studies have reported slightly better survival and the stage of HIV disease as the main predictor of survival on dialysis (9–13). In a small number of HIV-infected hemodialysis patients, we recently reported that use of highly active antiretroviral therapy has improved their survival (14). Although information regarding the antiretroviral therapy patients received in the study presented here was not available, we can speculate that the improved survival on dialysis observed is most likely the result of improved antiretroviral treatment. The data suggest that improvement in survival of HIV-infected ESRD patients has been more dramatic since 1997. Highly active antiretroviral therapy has been available much before this time. However, because the pharmacokinetics of the majority of antiretroviral drugs have not been thoroughly evaluated in patients with ESRD, the physicians could have been more hesitant to treat their patients with these drugs until more recently, when the experience with use of these medications has improved (25). Better management and prophylaxis against opportunistic infections and technical advancements in dialysis delivery may be other contributing factors in improvement in survival.

Although via life-table analysis we found that female dialysis patients had a better survival than male patients, the survival advantage was lost after adjusting for confounding factors in the regression model. Gender not being a factor in survival of these patients is consistent with a recent report of equal rates of progression to AIDS among men and women, despite the fact that initial viral loads were lower in women (26).

We did not find any differences in survival among different races. This is in contrast with the observations that black patients on dialysis have a better survival than whites (27,28). It is possible that unequal access to HIV care among the races could have made null the survival advantage seen in black patients on dialysis.

Although the survival of HIV-infected dialysis patients has improved, it is still very low compared with age-, gender-, and race-matched HIV-negative patients. The 1- and 2-yr survival of the HIV-negative patients was 87 and 79%, compared with 58 and 41% of HIV-infected dialysis patients. The data support that further improvements in the survival of these patients are likely to occur with development of better options for treatment of HIV infection.

There are several limitations of our study. Most important of all is the lack of information on plasma viral loads and total CD4 counts of the patients. These critical data were not available in the USRDS database and therefore could be a potential uncorrected confounding factors in the survival analysis. However, the fact that HIVAN is a manifestation of end-stage AIDS as reported by Winston *et al.* (29) and the large number of patients in our survival analysis attenuates the effects of stage of HIV infection on the survival data. The information on the antiretroviral therapy these patients received was also not available to us in this database. We can only presume that the improving survival is the result of better treatment options for these patients.

We conclude that survival of HIV-infected dialysis patients in the United States has remarkably improved. However, survival of these patients is still low compared with age- and gender-matched HIV-negative patients. Therefore, further improvement in their survival is likely to occur with improving treatment options for HIV infection.

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